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British Journal of Anaesthesia

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Volume XXIX No. 4 April 1957

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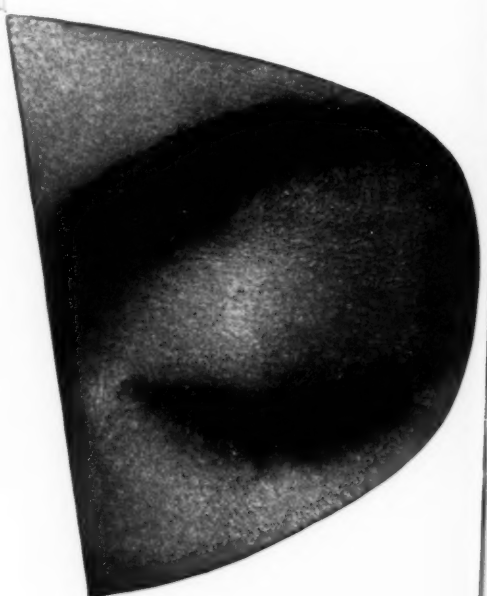

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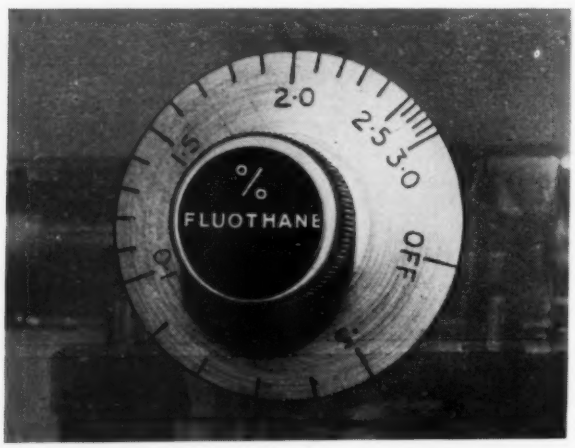

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BRITISH JOURNAL OF ANAESTHESIA

VOL. XXIX, No. 4 APRIL 1957

EDITORIAL

JUBILEE MEETING OF THE ASSOCIATION OF ANAESTHETISTS

Most national Societies of Anaesthetists hold some form of annual congress either on their own or jointly with a neighbouring country, or sometimes they do both. In this respect Britain has been an exception. The annual meeting of the British Medical Association, as far as its anaesthetic section is concerned, lasts only for one or at the very most two days, and at least in intention is supposed to interest general practitioners rather than specialists. The last meeting of anaesthetists on any scale held in this country was the International Congress held in 1951 in London. The decision, therefore, of the Association of Anaesthetists of Great Britain and Ireland to mark the Silver Jubilee of its foundation by a meeting in the nature of a congress will be especially welcome.

This congress will take the form of a three-day meeting on December 5, 6 and 7 next, at which there will be opportunities to give and hear papers on various aspects of anaesthesia as well as attractive social functions.

This occasion will give the Association an opportunity to welcome to this country many anaesthetists from overseas, and afford British anaesthetists the valuable opportunity for that conversational exchange of ideas which frequently is a most profitable aspect of such gatherings.

RECOVERY ROOMS

THE prospect of hospital rebuilding should encourage anaesthetists to formulate their ideas on the proper care of patients in the immediate pre- and postoperative periods. Anaesthetic rooms have for many years been a recognized part of the operating theatre blocks in this country, and their design and equipment have received some comment in recent years (Hewer, 1955). On the other hand, the provision of space for patients during the immediate postoperative recovery period is still a controversial subject which has recently been reviewed by Jolly and Lee (1957). Few people, however, can doubt that this time is fraught with potential danger, and evidence accumulates that some fatalities, and many less catastrophic but none the less troublesome complications, occur when the patient is transferred from the immediate supervision of the doctor.

The problems are largely due to the undesirable effects of anaesthesia of surgery, but are often aggravated, if not caused, by an inexperienced attendant failing to recognize or treat correctly the earliest signs of trouble. An imperfect airway occurs most frequently, but the bizarre results of anaesthesia inadvisably chosen or ill-administered, or of unexpected responses to a particular drug, must not be forgotten. Certain surgical procedures or pathological states may necessitate protracted resuscitation or special treatment immediately after operation, while the mechanical results of operations in the region of the airway or thoracic cage can create exceptional difficulties. However, even a normal recovery period may be made hazardous when it occurs at night time in a semi-darkened ward with the minimum of nursing staff available, while that irritating cacophony still not infrequently associated with emergence from anaesthesia—noisy delirium, retching, vomiting and the scuffling nurse—can hardly be rated a soothing nightcap for the other occupants of the ward. To add to these problems, the ancillary techniques of modern anaesthesia, such as hypothermia, often make special attention for the patient mandatory for some time after the operation has finished.

All these difficulties can be overcome by the provision of a recovery room near the operating

(*Continued on page 165*

Brit. J. Anaesth. (1957), **29**, 146

INVESTIGATION OF CEREBRAL DAMAGE FOLLOWING INDUCED HYPOTENSION

BY

OLE BERG, ERIC NILSSON AND ERIK VINNARS
University Hospital, Lund, Sweden

THE application of a method for the investigation of cerebral damage following anaesthesia using controlled hypotension was the subject of a preliminary communication in 1953.

Judging from the literature, cerebral function during and following induced hypotension has been studied mainly in three different ways, viz. by (*a*) cerebral haemodynamic measurements by the method of Kety and Schmidt (1948); (*b*) electro-encephalography; and (*c*) psycho-physical examination with the flicker fusion method of Berg (1949).

(*a*) Investigations by cerebral haemodynamic methods have given contradictory results.

Crumpton and Murphy (1952), Dewar, Owen and Jenkins (1953), and Stone, MacKrell and Wechsler (1955) showed that in nonanaesthetized patients no changes occur in the cerebral circulation until after a reduction of anything up to 40 per cent in the arterial blood pressure because of a corresponding decrease in the vascular resistance. Crumpton and Murphy, and Dewar, Owen and Jenkins carried out their investigations on patients with arterial hypertension. Stone and co-workers found the cerebral blood flow to be unchanged also on combination of hypotension and elevation of the head end of the table by 15°. In their examinations the blood pressure was reduced by ganglionic block.

Kety (1950), on the other hand, found that in hypertensive patients with spinal sympathetic block a 30 per cent decrease in the blood pressure was followed by a decrease in the cerebral blood flow because of inadequate vasodilatation.

Meyer and Morris (1955) and Saunders (1954) found that a 40 per cent reduction in the blood pressure by ganglionic block was not completely compensated by vasodilatation, but that the uptake of oxygen by the brain nevertheless persisted unchanged with an increased difference between the oxygen tension of arterial and venous blood. Hughes (1955) made similar observations in patients under light thiopentone anaesthesia.

Saunders reduced the blood pressure to 60 mm Hg in patients in the erect position. This reduction did not cause any loss of consciousness, but it did produce signs of slight cerebral ischaemia.

(*b*) Bromage (1953) traced electro-encephalograms of three nonanaesthetized subjects with controlled hypotension and lying on the table with the head end elevated. Convulsions and pronounced electro-encephalographic changes were noted in two of them. Van Bergen and associates (1954) traced electro-encephalograms of patients under light thiopentone anaesthesia and then during reduced blood pressure. They found that as a rule all activity ceased at a systolic pressure of 55 mm Hg.

(*c*) The psycho-physical method we used was the flicker fusion test described by Berg (1949). In some of the cases we also made electro-encephalograms simultaneously and compared the results. The electro-encephalograms were traced and interpreted at the Department of Neurology.

TECHNICAL DATA

Intermittent light of a given frequency and intensity is perceived as a flicker. By increasing the frequency or the intensity the subject will perceive the flicker as a continuous light. That is known as the flicker fusion phenomenon, and the stage at which the flicker appears as a continuous light is known as the critical threshold value for flicker fusion (c.f.f.). The c.f.f. can be determined by varying the frequency of the light or its intensity. In our investigations we varied the intensity.

The c.f.f. is usually constant for a given person and its normal range of variation is narrow. Training does not influence the c.f.f. In routine examinations the subject fixes the eyes centrally on the light. By determining the c.f.f. it is possible to check the function of the retinocortical pathways and possibly also a large region of the brain in intimate contact with the visual cortex.

Determination of the c.f.f. may be regarded as a functional test of the central nervous system (Berg, 1949). Berg improved the method by the introduction of the use of hexobarbitone. According to this method the patient receives 50–100 mg hexobarbitone, according to age and body-weight. This does not increase the c.f.f. of normals, and then the test is said to be negative. In the presence of diffuse cerebral injury, such as acute head injury, acute encephalitis or acute neurosyphilis, the c.f.f. is decreased, and if it remains so for at least eight minutes the test is said to be positive.

In the presence of slight head injury, the test may be positive for 2 or 3 days; if the injury is severe, for 2 or 3 weeks. The duration of a positive test, i.e. the number of days before it turns negative, varies with the severity of the injury (Berg, 1949; Åkerlund, 1952). When the injury has healed the test turns negative.

Cerebral hypoxia produces a diffuse cerebral injury which heals after the hypoxia has passed off. In this respect hypoxia is comparable to acute head injury and therefore the flicker fusion test can be used for the investigation of such cases (Berg, 1955).

PLAN AND RESULTS OF THE INVESTIGATION

The purpose of the investigation was confined to an elucidation of cerebral function and any complications due to disturbed cerebral function. General physiological reactions of the circulatory apparatus, of the liver or of the kidneys, for example, thus lay beyond the scope of the study. Therefore the present material embraced only a limited portion of all the patients operated on under hypotension, since the neurosurgical material and those cases in which operation on the face implied a transient disturbance of vision were naturally not included. In addition a few patients were unable to co-operate.

TABLE I

Hexobarbitone tested hypotensive patients

Number of cases	Negative flicker fusion test	Positive flicker fusion test	Pos. test >6 days
73	35	38	10
	CONTROLS		
30	30	0	0

The material consisted of 73 surgical patients in whom hypotension was induced for 20–90 minutes during anaesthesia.

In about one-third of the patients ganglionic block was induced with hexamethonium, trimetaphan being used for the remainder. Of the 73 patients (table I), the hexobarbitone test was negative in 35 and positive in 38, suggesting a varying degree of cerebral injury probably due to the period of hypotension, to the anaesthesia or to the operation. Of the 38 with positive test, the

TABLE II

Correlation between diagnosis and outcome of hexobarbitone test.

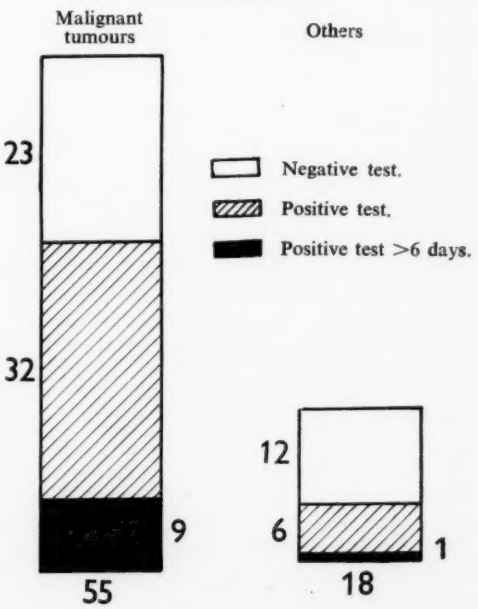


TABLE III

		Sex		Age (years)		Ganglion blocking agent	
		♂	♀	25–49	50–68	Hexa-methonium	Trimeta-phan
Negative flicker fusion test	(35)	13	22	21	14	11	24
Positive flicker fusion test	(38)	23	15	24	14	12	26
Pos. >6 days	(10)	8	2	5	5	4	6
Total number		36	37	45	28	23	50

test persisted positive for more than 6 days. A positive test of this duration suggests a cerebral injury comparable to moderate concussion of the brain.

In an attempt to check whether the flicker fusion test is influenced by anaesthesia and the operation only, i.e. without any extra strain implied by a period of hypotension, a control series was studied. This control series consisted of 30 patients operated on for biliary diseases and anaesthetized with hexobarbitone in an induction dose, which was followed by N_2O-pethidine-d-tubocurarine chloride. In all of these patients the test carried out after operation was negative.

The material is classified according to diagnosis in table II.

It is apparent that the majority (55) of patients had malignant diseases. In only 18 was the disease not malignant. It is also clear that the flicker fusion test was positive about twice as frequently among those with malignant diseases. Thus it was positive for more than 6 days in 9 of the 10 patients with cancer. In these 9 patients with such severe cerebral injury the fundamental disease was very advanced. Therefore the high frequency of positive tests in the cancer group might be ascribed in part to general biological changes.

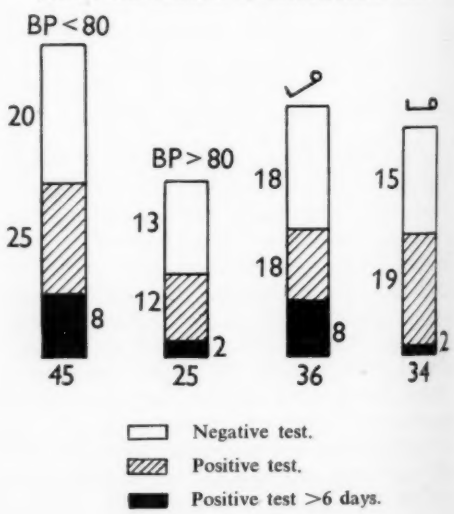
The material comprised 36 males and 37 females (table III). The test was positive for 23 males but for only 15 of the females. In the group of 10 patients that had severe cerebral injury and for whom the test was found to be positive for more than 6 days the difference with sex was still more striking, namely 8 males as against only 2 females. It is difficult to offer any explanation for this higher sensitivity of males to hypotension, but Beecher and Todd (1954), as well as Gordh (1950), showed that females tolerate operations better than males.

Of our patients, 45 were above 50 years of age and 28 below. One might perhaps expect a higher frequency of positive tests in the higher age group, primarily because of the changes in the blood vessels with age. In advanced age the vessels are probably not able to adapt themselves to hypotension to the same extent as in younger patients. Strangely enough, however, the test was positive with equal frequency in both groups, even among those with fairly severe cerebral injury.

As to the two blocking agents, hexamethonium and trimetaphan, no difference was found in the frequency with which the test was afterwards positive, i.e. with which the use of the drug was followed by slight cerebral injury. Therefore it is probably the duration of hypotension rather than the choice of drug that is decisive. How-

TABLE IV

Correlation between blood pressure, respiration, posture and outcome of hexobarbitone test.



ever, we definitely prefer trimetaphan because its effect is short and therefore permits better control of the period of hypotension.

If we now consider the blood pressure during the period of hypotension and take 80 mm Hg as a limit (table IV), we see that positive tests were equally frequent on either side of this level. But of those tests that were positive for more than six days, as many as 8 were in the group with a blood pressure below 80 mm Hg. A a similar difference was found on comparison of the patients according to the position of the operating table, i.e. horizontal and head end raised. The ratio between the frequency of positive and negative tests did not differ with the position of the operating table. But here, too, the interesting observation was made out of 10 with prolonged positive test, 8 belonged to the group that had lain on the table with the head end elevated.

On consideration of these two factors together, i.e. the blood pressure and the position on the operating table, it was found that the majority of those with a prolonged test (7 out of 10) had had a pressure below 80 mm Hg and had been lying on a table with the head end raised (see table V). It is thus obvious that in patients with a blood pressure below 80 mm Hg the induction of hypotension involves greater risks if the head end of the table is elevated. The frequency of positive tests did not vary with the duration of hypotension within the limits studied (20–90 minutes): therefore, 20 minutes hypotension appears to be sufficient to produce the injuries demonstrated.

TABLE V

Correlation between blood pressure, posture, and outcome of hexobarbitone test.

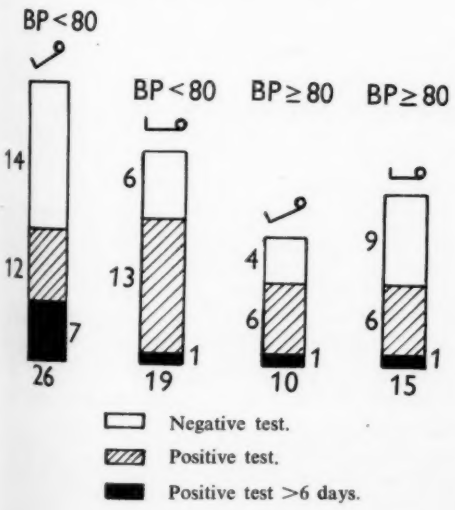


TABLE VI

	E.E.G. after operation		
	Patho-logic	Normal	Total
Negative flicker fusion test (35)	2	9	11
Positive flicker fusion test (38)	9	8	17
Pos. >6 days (10)	4	3	7

The results of the flicker fusion tests were compared with electro-encephalograms in 28 cases (table VI). Of these 28 cases, the flicker fusion test was negative in 11. In 9 of them the e.e.g. showed abnormalities, in the remaining 2 it was of normal appearance. Of the group of 17 patients with a positive flicker fusion test, the e.e.g. was normal in 8 but showed pathologic changes in the remaining 9. Of the 10 patients with a positive flicker fusion test for more than 6 days, 7 were included in the electro-encephalographic study and, strangely enough, the e.e.g. was of normal appearance in as many as 3 of them. This suggests that the flicker fusion test might be more sensitive than electro-encephalography for demonstrating functional disorders of the brain.

SUMMARY

Investigation of the effect of induced hypotension showed that: (*a*) in about 50 per cent of the patients the hexobarbitone flicker fusion test was positive and suggested a varying degree of diffuse cerebral injury; (*b*) patients with advanced cancer are particularly vulnerable; (*c*) males are more vulnerable than females; (*d*) a decrease in the blood pressure below 80 mm Hg in combination with elevation of the head end of the operating table considerably increases the risk of cerebral injury.

The cerebral injuries demonstrated in the present investigation were transient and slight. Even in the 10 patients with more severe injury, the symptoms soon disappeared.

These injuries were comparable to those of hypoxia and it is known that repeated periods of hypoxia can have a cumulative effect.

It is suggested that patients should not be submitted repeatedly to hypotensive anaesthesia without an interval long enough to permit recovery from any injury sustained.

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ASSOCIATION OF ANAESTHETISTS OF GREAT BRITAIN AND IRELAND

JUBILEE MEETING

The Association of Anaesthetists of Great Britain and Ireland is celebrating the twenty-fifth anniversary of its formation this year, and is holding its Annual Meeting on December 4, 5, 6 and 7, 1957, at the Royal College of Surgeons, Lincoln's Inn Fields, London, W.C.2.

The provisional programme is as follows:

Wednesday, December 4
Evening: The Association will hold a Cocktail Party to welcome those overseas visitors who will attend the meeting.

Thursday, December 5
Morning session: Papers.
Afternoon session: Annual General Meeting. Frederic Hewitt Lecture.
Evening: Annual Dinner.

Friday, December 6
Morning session: Papers.
Afternoon session: Papers. Meeting of the Section of Anaesthetics of the Royal Society of Medicine.
Evening: Cocktail Party given by the Faculty of Anaesthetists. Dance.

Saturday, December 7
Morning session: Symposium.

Throughout the Meeting there will be a Scientific Exhibition and a Trade Exhibition.

The final date for submission of papers for presentation at this meeting is June 1, 1957.

Further particulars will be available later on application to the Secretary, Association of Anaesthetists of Great Britain and Ireland, 45 Lincoln's Inn Fields, London, W.C.2.

Brit. J. Anaesth. (1957), **29**, 151

THE ROLE OF THE CANINE LIVER IN THE DETOXICATION OF D-TUBOCURARINE CHLORIDE, GALLAMINE TRIETHIODIDE AND LAUDEXIUM

BY

ALAN L. STEAD*
Alder Hey Children's Hospital, Liverpool

AND

W. H. HORNER ANDREWS
St. Mary's Hospital, Paddington, London

INTRODUCTION

THOUGH muscle relaxants are extensively used in modern anaesthetic practice, information about their fate in the body is meagre and often conflicting. It is the object of this paper to elucidate the role played by the liver in the detoxication of the competition blocking agents.

The investigation presented two major problems:

(*a*) A method of liver perfusion which involved the minimum of physiological disturbance.

(*b*) The extraction from and assay of the quantity of relaxant in the perfusate.

METHOD

Method of Liver Perfusion.

Perfusion of the canine liver was performed by the method described by Andrews (1953). After anaesthetizing with thiopentone a tracheotomy was performed and artificial respiration started with a Starling respiratory pump. An incision was then made from the topmost part of the sternum to the symphysis pubis and both thorax and abdomen opened. A cannula was inserted into the thoracic inferior vena cava pointing downwards towards the liver, and blood allowed to drain into a reservoir from which it was pumped through a Hooker oxygenator to the inflow cannulae. The superior mesenteric artery was now clamped and the portal vein rapidly cannulated, the flow being started immediately. The time between starting the portal flow and the cannulation of the inferior vena cava was usually 1 minute or less. The hepatic artery was next cannulated, and the arterial flow started. The inferior vena cava was now clamped below the liver and all blood vessels in the porta hepatis excepting the hepatic artery and portal vein were ligated. The perfusion pressures used were: portal venous 7–12 cm blood; hepatic arterial about 110/100 mm mercury. Oxygenated blood was supplied to both vessels.

In large dogs whole blood only was used, the anticoagulant being heparin. In smaller dogs the volume of circulating fluid was sometimes increased by addition of polyvinyl pyrrolidone (3 per cent) in Ringer Locke solution. In many experiments this solution was added to the general circulation of the dog before clamping the abdominal inferior vena cava in order to "wash out" blood contained in the blood vessels. Haemoglobin values of over 12 g per cent were almost always obtained.

The quantities of d-tubocurarine chloride, laudexium and gallamine triethiodide added to the preparation were calculated to give a concentration in the perfusate not dissimilar from that used in clinical practice.

After the addition of a drug a period of 3 minutes was allowed to ensure uniform distribution throughout the preparation. Samples of blood were then withdrawn at 20-minute intervals for a period of 1 hour.

Verification of Method.

Whilst no perfused organ can be considered entirely normal, there is evidence that livers per-

* Work carried out while Dr. Stead was a Cow and Gate Fellow, attached to the Department of Child Health, Liverpool University.

fused by this method are probably not grossly abnormal. Nielsen (1933) and Lundsgaard, Neilsen and Ørschov (1936), using a similar method, found that glucose in the perfusing fluid slowly disappeared, though they had difficulties in dogs owing to swelling of the liver. In our experiments no difficulties due to swelling occurred and it was shown that the blood glucose concentration, high at the start of the perfusion, fell regularly to a more normal concentration, owing presumably to glycogen formation or to tissue metabolism. Without the addition of drugs, livers could be kept in excellent condition for 5 hours and, in a similar series of experiments using a slight modification of technique, bile secretion has continued for over 6 hours. Reasons for believing the liver to be substantially normal are also presented by Andrews, Hecker, Maegraith and Ritchie (1955). It is probable that the enzyme systems of the liver were not grossly affected and destruction by the parenchyma of various substances such as adrenaline, acetylcholine and histamine was rapid, and the removal and excretion of sulphobromophthalein was within normal limits.

d-Tubocurarine undoubtedly affected the liver causing swelling and congestion. These effects are similar to those produced by histamines, and could be accounted for by histamine release. It also decreased the oxygen usage, but in only one of the experiments did this effect last longer than 10–15 minutes. In another series of experiments it was shown that addition of the histamine releaser compound 48/80 produced the same vascular effect and that mepyramine maleate largely antagonized the effects of both d-tubocurarine and of compound 48/80. Vascular changes due to gallamine or laudexium were considerably less marked.

Methods of Extraction and Assay.

Extraction. The method used to extract and assay the quantity of relaxant present in each blood sample was similar to that described by Mahfouz (1949). Essentially it is a measurement of the antagonism between acetylcholine and the neuromuscular blocking agents.

After collection the cells and plasma were separated by centrifuging. Low speeds avoided haemolysis. It was shown by Mahfouz (1949) and confirmed by us that cellular extracts contain no competition blocking agents. Only the quantity of relaxant present in the plasma was, therefore, estimated.

The separated plasma was added drop by drop to 12 ml of an acid alcohol solution. This had been prepared by the addition of 0.1 ml normal solution of hydrochloric acid to 250 ml of absolute alcohol. The solution was thoroughly shaken after each drop. The precipitate so formed was filtered and washed with 38 ml of acid alcohol. The filtrate was evaporated to dryness on a water bath using a partial vacuum. The residue was dissolved in Ringer's solution.

Assay. A frog's rectus muscle was isolated and placed in a water bath of 2.2 ml capacity. The bath was aerated by a continuous stream of oxygen bubbles. The muscle contractions were recorded on a smoked drum. The mechanical amplification of the muscle contraction was about 10 and the tension in the muscle 3 g.

A constant dose of acetylcholine, usually of the order of 1 μg, was added to the bath every 4 minutes. It was allowed to act for 1½ minutes. For the remaining 2½ minutes the acetylcholine was removed from the bath and the preparation allowed to relax. The Ringer solution in the bath was changed 9 times, the time of change being constant in each 4-minute cycle.

When the response to the acetylcholine was constant a suitable volume of extract was added 60 seconds before the acetylcholine and its effect on the subsequent muscle contraction recorded. The effect of the extract was compared with that of known concentrations of the muscle relaxant under examination.

When drugs are added at a constant time interval the effect produced in a given constant time is regularly related to the dose and can be taken as an index of the potency of the solution. Throughout the experiment there was a slight deterioration in the response of the muscle to doses of acetylcholine. A similar amount of extract or muscle relaxant, however, always produced the same percentage depression of muscle contraction.

Accuracy of the Method.

In pilot experiments it was found possible to extract 75–90 per cent of a known quantity of

relaxant added to a blood sample. It was not found possible to detect less than 0.2 μg of d-tubocurarine chloride.

RESULTS

Three experiments were carried out with each relaxant. The results so obtained are given in table form. Table I shows the concentration of d-tubocurarine chloride in the perfusate when 6 mg were added to the liver preparation; table II, the concentration of gallamine triethiodide when 40 mg were added to the preparation; and table III, the concentration of laudexium when 10 mg were added. Three dogs were used for each drug under assay.

TABLE I

	Concentration of d-tubocurarine in μg per ml of plasma			
Time in minutes	3	23	43	63
Dog 1	5.4	5.8	3.4	4.2
Dog 2	8.3	6.6	8.6	8.0
Dog 3	5.6	6.3	5.2	7.4

TABLE II

	Concentration of gallamine triethiodide in μg per ml of plasma			
Time in minutes	3	23	43	63
Dog 1	33.6	45.8	41.6	40.8
Dog 2	41	50	51	45
Dog 3	57.6	55.8	52.9	53.8

TABLE III

	Concentration of laudexium in μg per ml of plasma			
Time in minutes	3	23	43	63
Dog 1	16.6	10.5	20.0	13.2
Dog 2	10.2	8.8	9.8	8.6
Dog 3	10	6.0	6.0	6.0

These results show, that after perfusion for 63 minutes through the physiologically intact canine liver, there is no material alteration in the concentration of d-tubocurarine chloride, gallamine triethiodide or laudexium in the perfusing fluid. This suggests that in the dog the liver itself plays no part in the detoxication of the competition blocking agents.

DISCUSSION

Previous workers assessing the role of the liver in the detoxication of competition blocking agents have used four different methods of study.

In vitro experiments were made by Albanese (1901) and Pick and Richards (1948). These workers showed that curare alkaloids lose their activity in homogenates of ox and mouse liver. Mahfouz (1949), however, recovered from mouse liver all the curare added to it.

Roger in 1886, compared the effect of a standard dose of curare injected into a peripheral systemic vein with the same dose injected into the portal system and thus traversing the liver before entering the arterial system. He showed that the paralysing dose of curare is larger when the drug is injected into the mesenteric than into the femoral vein. Gaglio (1888) and Sauer (1891) were, however, unable to confirm this. Roger's results could be explained if the liver is capable of withholding curare from the general circulation without, necessarily, detoxicating it.

Several workers have extirpated 70–90 per cent of the liver. Gaglio (1883) and Albanese (1901) concluded that this procedure hastened muscle paralysis when the curare was administered orally. Everatt (1948) and Mahfouz (1949) were, however, unable to detect any increase in sensitivity to d-tubocurarine in partially hepatectomized rats. Kelly, Shideman and Adams (1947) have shown,

moreover, that partial hepatectomy is not a dependable method of eliminating the liver as an organ of detoxication.

Liver damage has been effected by the creation of an Eck fistula or porto caval anastomosis. Rothenburger and Winterburg (1905) found that the creation of an Eck fistula in dogs did not change their sensitivity to curare. Polimanti (1914) concluded that, under such conditions, smaller doses were required for total muscle paralysis. Kelly and Shideman (1949) using the Eck fistula concluded that the liver participates in the detoxication of Intocostrin unless the dose used is very small.

The results of previous workers, therefore, are conflicting. Laboratory workers who have employed the technique of liver damage or extirpation of the liver have assumed that an altered response to a muscle relaxant is due to a decrease in the capacity of the liver to detoxicate the relaxant. These observed responses may be due, however, to other causes. It is possible that by liver dysfunction some of the body's enzyme systems are deranged. These alterations may affect the responses of the myoneural junction to acetylcholine and to antidepolarizing agents. The role of the liver in maintaining the equilibrium of the acetylcholine-cholinesterase mechanism is not clearly defined. Liver damage is frequently associated with low pseudocholinesterase levels (Wilson et al., 1952) and in clinical practice these patients may be resistant to d-tubocurarine chloride (Dundee and Gray, 1951).

The relationship between pseudo and true cholinesterase at the myoneural junction is unknown. Heymans et al. (1948) have suggested that where the pseudocholinesterase activity is low, there is an increased sensitivity to acetylcholine at the motor end plate. It is possible, therefore, that liver damage, by its effect on the acetylcholine-cholinesterase mechanism, may alter the response of the myoneural junction to muscle relaxants. This altered response, may, in fact, be caused by an alteration of the myoneural conducting mechanism. It need not be related to any action of the liver on the muscle relaxant.

In this paper the problem has been approached more directly and an attempt has been made to eliminate the peripheral effects which a damaged liver may produce and which inevitably confuse the picture.

SUMMARY

The role of the canine liver in the detoxication of competition blocking agents has been determined by direct perfusion of the liver and biological assay of the perfusate.

The results indicate that the canine liver plays no part in the detoxication of d-tubocurarine chloride, gallamine triethiodide, and laudexium in concentrations similar to those used in clinical practice.

The results of previous workers have been discussed and a possible explanation offered to account for their conflicting results.

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BOOK REVIEW

Anaesthesia for Surgery of the Heart. By Kenneth K. Keown, M.D. Published by Charles C. Thomas, Springfield, Illinois. Also published simultaneously in England by Blackwell Scientific Publications. Price 27*s*. 6*d*.

Since the field of cardiac surgery is being widened every year the introduction of a book on this branch of anaesthesia is a timely move.

Dr. Keown, who is well known as the Associate Professor of Anesthesiology at the Hahnemann Medical College and Hospital, Philadelphia, has been engaged in " cardio-anesthesiology " in the Bailey Thoracic Clinic for the last 10 years.

The arrangement of the subject matter in this book of some 100 pages is highly commendable. The first 24 pages deal with pre-operative and anaesthetic management. This is followed by a chapter each on Cardiac Irregularities, Complications during Anaesthesia, and Post-Anaesthetic Management. The last 60 pages of the book deal, chapter by chapter, with all the conditions amenable to surgery. The physiological and clinical features of each abnormality are briefly enumerated, followed by an outline of the various investigations. The results in each case include a chart giving data obtained by cardiac catheterization. The scope of surgery and the anaesthetic management appropriate to each condition are then discussed. While making due allowance for the different drugs in current use in the American continent, it is difficult to reconcile some of the advice given. Few will care to administer 5 per cent sodium thiopentone solution intramuscularly to inadequately sedated infants and children, despite the warning to avoid the sciatic nerve. The administration of decamethonium bromide or suxamethonium to a conscious patient before the administration of thiopentone seems paradoxical when advice is given elsewhere " to decrease the fear of the patient ". The use of muscle relaxants after intubation is not encouraged and controlled respiration is facilitated by repeated injections of thiopentone. This is emphasized by the advice to use only 100 per cent oxygen for inhalation except where the B.P. after positioning the patient is over 100 mm Hg systolic and can only impose an unnecessary strain upon the patient's already impaired cardiac reserve. Viewed in this light the advice that " individuals with profuse secretions of the tracheobronchial tree demand either overdosage with thiopentonal sodium or . . ." seems most unwise.

It is inevitable that in a new book a few mistakes will be found, but the frequent lack of precision in terminology is unexpected. " Infants from one month to six years of age " may perhaps be excused, but the description of decamethonium bromide and succinylcholine hydrochloride as " curare-like " drugs would hardly be expected of a D.A. candidate. The inference on pp. 93–94 that oxygen is a drug is unfortunate in a book which starts off so well by emphasizing the essentials of anaesthesia for this branch of surgery as " adequate oxygenation, constant evaluation, and a light plane of anaesthesia ".

In short, this book, which is well produced and set out, will commend itself to the British anaesthetist more as a textbook of surgical cardiology than as a guide to anaesthetic technique.

Tom Dinsdale

Brit. J. Anaesth. (1957), **29**, 156

THE INFRARED ANALYSIS OF CARBON DIOXIDE DURING ANAESTHESIA *

BY

P. W. RAMWELL

Department of Anaesthesia, University of Leeds

THE method of estimating carbon dioxide by infrared absorption is being used more intensively, and its application has been extended from the laboratory to the poliomyelitis ward, operating theatre and recovery room. It is important that one should possess a clear idea of the potential sources of error which are likely to occur under these different circumstances. This type of analyzer has been described by Woolmer (1953).

It is generally known that nitrous oxide and other gases possessing absorption bands adjacent or overlapping those of carbon dioxide, may cause false high readings. This is overcome by using the gas as an optical filter (Bracken and Sanderson, 1955). Some of the anomalies present in a recent paper (Elam, Brown and Ten Pas, 1955), appear to be attributable to this source.

A second error caused by the addition of water vapour to the expired air by the lungs is minimized by maintaining the analyzer above 38°C. In most instruments the two opposing errors, due to the dilution of the dry gas and that due to water vapour possessing similar absorption bands to those of carbon dioxide, nearly cancel out each other. The wet gas causes a discrepancy of usually not more than 0.03 per cent carbon dioxide for a 5 per cent concentration. Generally the discrepancy is barely detectable.

A third error (Stow, 1952) not widely known is that due to the broadening of the absorption bands of carbon dioxide by the diluent gas (Coggeshall and Saier, 1947; Ramwell, 1957). Such a broadening of the absorption band will increase the optical density of carbon dioxide to infrared radiation causing the analyzer to give a false high reading. Thus 5 per cent carbon dioxide in oxygen is estimated at 5.4 per cent in an infrared analyzer when the oxygen is replaced by nitrogen (fig. 1). Nitrous oxide and cyclopropane also cause a similar error but of much greater magnitude (figs. 2, 3). When the analyzer is standardized with 5 per cent carbon dioxide in oxygen, similar concentrations (prepared manometrically in tonometers—fig. 4) in nitrous oxide and cyclopropane cause the analyzer meter to read 6.2 per cent and 6.7 per cent respectively, even though the diluent gas is used as an optical filter (fig. 5).

Göpfert and Henneberg (1957) report a decrease in the value of the alveolar plateau when the subject breathes oxygen, and when air breathing is resumed the plateau returns to its normal value. This observation is probably due to oxygen causing less absorption band broadening than does the standardizing diluent gas, which presumably was air. Some authors (Collier, Affeldt and Farr, 1955) employ calibrating cylinders of special "alveolar" concentrations. These are expensive and carbon dioxide in air is cheaper and causes but little error.

The error due to absorption band broadening by the diluent gases can also be demonstrated by making up mixtures of carbon dioxide in oxygen, cyclopropane and nitrous oxide with the standard anaesthetic machine, and passing them through the analyzer in a manner analogous to that illustrated in figure 6.

During inhalation anaesthesia, the error may be overcome by standardizing the instrument with carbon dioxide in air or oxygen and employing calibration curves, previously prepared in the laboratory, for each gas mixture (fig. 2). Care must be taken to adhere to the composition of the diluent gases of the calibrating curve during the period of

* The cost of this research was defrayed in part by a grant from the Medical Research Council.

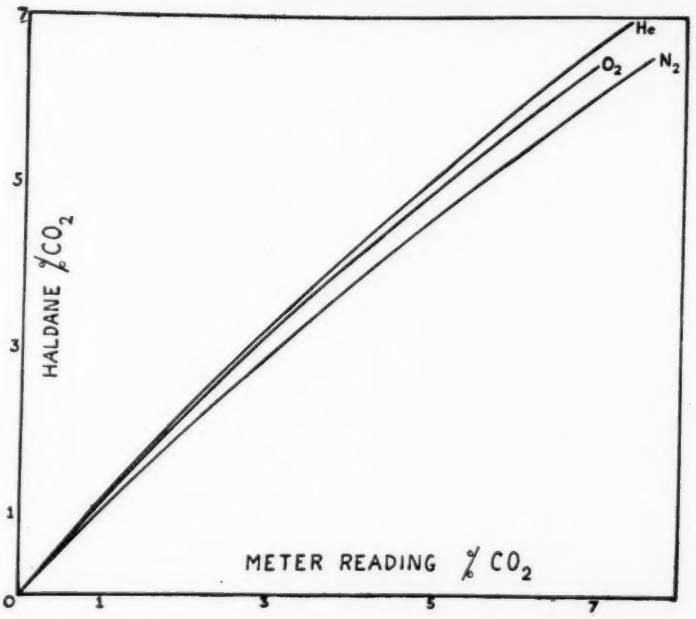

FIG. 1

These gas mixtures were prepared in Douglas bags and passed through the analyzer at the same time as a sample was taken for estimation by Haldane's method.

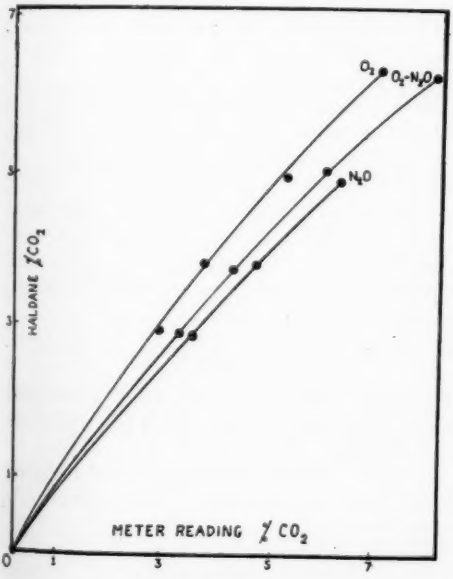

FIG. 2

Calibration curves for carbon dioxide in oxygen, carbon dioxide in nitrous oxide and carbon dioxide in a 50:50 nitrous oxide-oxygen mixture.

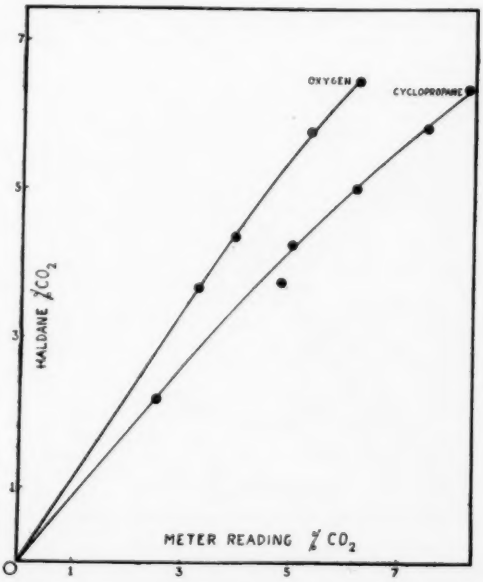

FIG. 3

The carbon dioxide concentrations in this figure, and figures 2 and 5 were prepared by the manometric method illustrated in figure 4. In all the figures the instrument was standardized with carbon dioxide in oxygen.

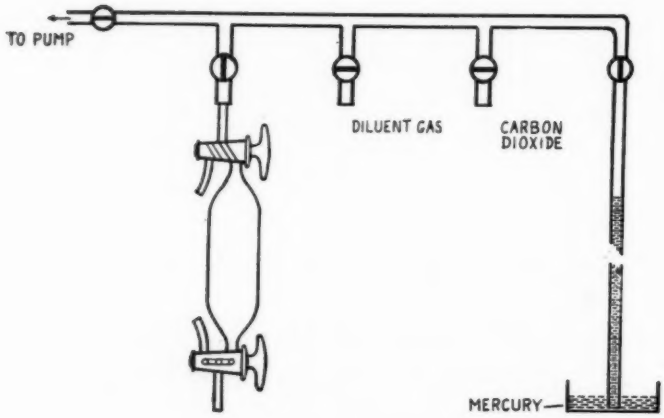

FIG. 4
Gas mixtures were also prepared by evacuating a tonometer, bleeding carbon dioxide into it via a manifold, noting the pressure drop and then bringing the system to atmospheric pressure with the appropriate diluent gas. This method was checked by Haldane's method where the nature of the diluent gas permitted.

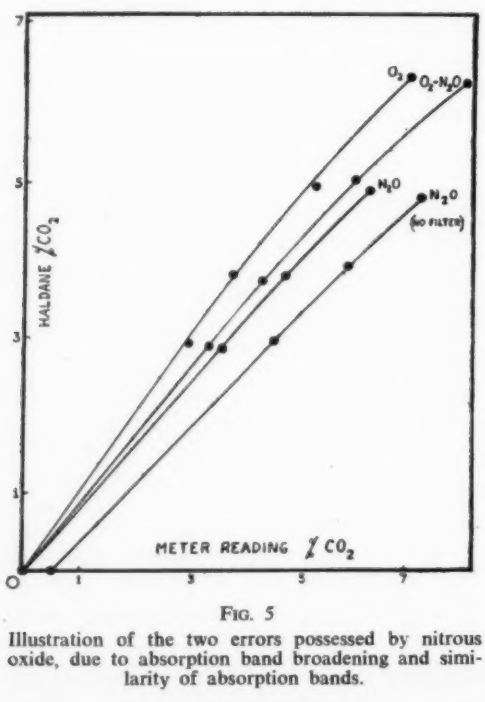

FIG. 5
Illustration of the two errors possessed by nitrous oxide, due to absorption band broadening and similarity of absorption bands.

anaesthesia, which means that rebreathing of the gas mixture must be avoided. There is not a linear relationship between the percentage composition of the diluent gases and the apparent change in the concentration of carbon dioxide.

The errors mentioned provide a more comprehensive basis for the criticisms by Collier et al. of other workers employing analyzers during anaesthesia (Siebecker, Mendenhall and Emmanuel, 1954).

Other gases possessing low moments of inertia are also subject to absorption band broadening. One may expect errors, similar to those demonstrated with carbon dioxide, when employing infrared methods of estimating nitrous oxide.

CONCLUSIONS

Even when used as an optical filter, anaesthetic gases are a source of error in the infrared estimation of carbon dioxide.

The error caused by the presence of anaesthetic gases can be minimized by the choice of an appropriate calibrating gas mixture.

ACKNOWLEDGMENTS

I am grateful to Dr. R. P. Harbord for his encouragement, to Mr. L. Grant for his skilled technical

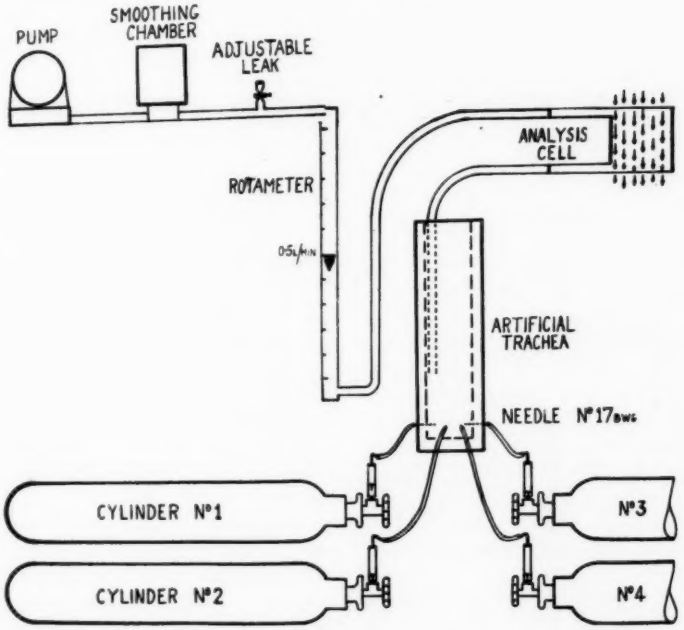

FIG. 6
Method for calibrating the analyzer with cylinders containing different concentrations of carbon dioxide in air or in oxygen.

assistance and patience, to Professor A. Hemingway, Department of Physiology, and Dr. W. M. Pols of Utrecht for allowing their infrared analyzers to be used to confirm some of the errors.

I am grateful to the British Oxygen Company for loaning equipment and making up special gas mixtures in cylinders.

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THE RESISTANCE OF ENDOTRACHEAL CONNECTORS

BY

S. GALLOON

Department of Anaesthetics, University of Glasgow

THE added resistance to breathing offered by the various components of the anaesthetic circuit is a major problem facing the anaesthetist, particularly in paediatric anaesthesia, and yet one which has produced very little comment in the literature. Macintosh and Mushin (1947) deal briefly with the problem, and Macon and Bruner (1950) discuss the question of the flow of gases through endotracheal tubes. In 1954 Orkin et al. investigated the resistance of soda lime canisters, and endotracheal catheters and adapters, whilst Hunt (1955) described the resistance of disc valves and canisters.

All these writers used a steady flow of gas at varying rates to measure the resistance, but Hamilton and Eastwood (1956) used a pneumotachograph screen and an electromanometer (recording airway pressure readings) to show changes occuring in the volume and pattern of ventilation as the result of introducing resistance into the air flow, in the form of soda lime canisters and valves.

The only work mentioning endotracheal connectors apart from Macintosh and Mushin, is that of Orkin et al., and they, of course, were concerned with American fittings. They stress the fairly obvious fact that the narrowest part of the circuit, and therefore the part with the biggest resistance, is the endotracheal connector (or adapter, as they call it) and it was felt that actual measurements of the resistance of British connectors would be a useful addition to the knowledge of anaesthetists.

THE THEORY OF RESISTANCE

For a given volume of a gas to pass through a tube in a certain time, there must be a difference in pressure between the two ends of the tube; this pressure difference is a measure of the resistance to be overcome when a gas is forced or drawn through the tube, so that the resistance of a length of tubing may be defined as the pressure difference between the entry and exit ports, under certain conditions.

Where the outlet from the tube communicates with the open air, the pressure here is obviously atmospheric, so that a manometer placed in the position shown in figure 1 will give the pressure difference and thus the resistance of any tubing that may be connected to it.

The resistance of a length of tubing depends on:

(1) The volume of gas flowing through in unit time. According to Macintosh and Mushin (1947), in an adult breathing 8 litres per minute quietly, the maximum flow rate of air during normal inspiration reaches 25 litres per minute, and they use this latter rate to measure experimentally the resistance of endotracheal connectors. This figure may be on the low side, however, as Proctor and Hardy (1949) found an average peak inspiratory velocity (in normal patients) of 35 litres per minute; similarly Cherniack et al. (1952) give a figure of 35.5 litres per minute, and Mead and Whittenberger (1953) 30–50 litres per minute for quiet breathing.

(2) Viscosity of the gas. The flow rate is inversely proportional to the viscosity.

(3) The diameter of the tube.

(4) The length of the tube.

(5) The nature of the flow. Osborn Reynolds (1883) was the first to demonstrate the two types of flow of a fluid or gas in a tube, the smooth orderly type known as laminar, and the disorderly type known as turbulent, which may be local or general.

In anaesthetic practice it can be shown that the volume flow rates of inspired gases are below those which result in general turbulence, but areas of local turbulence (and therefore increased resist-

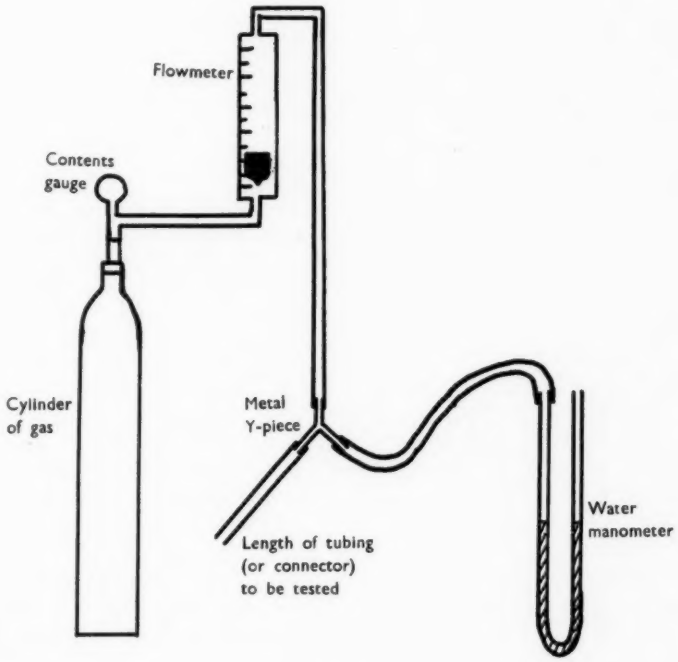

FIG. 1
Apparatus for measuring resistance experimentally.

ance) can occur at a flow rate well below the critical—these local areas are produced by the unavoidable irregularities, bends, corners and constrictions which make their appearance in any anaesthetic set-up.

With the almost universal acceptance of the principle of large bore corrugated breathing tubes, and the increasing tendency to pass an endotracheal tube on more and more patients, the narrowest part of the anaesthetic circuit has become the connector joining the endotracheal tube to the expiratory valve. It would seem that this narrowness, together with the often acute angle of the connector, is responsible for much of the local turbulence and therefore of the resistance of the circuit, and this investigation was undertaken to determine whether there was any difference in the resistance offered by various connectors.

METHOD

The arrangement shown in figure 1 was used to measure the resistance of the connectors, with a constant flow rate of gas of 25 litres per minute, the figure given by Macintosh and Mushin. Although, as pointed out before, this may be on the low side for peak rates of flow during the respiratory cycle, it was felt that this would not affect the final conclusions, which are concerned with a comparison of different connectors, rather than the absolute resistance of any particular connector.

The connectors tested were those in more common use in this country and table I gives a list of them.

The final figures given are the average of 5 individual readings taken on different occasions and table II is an example showing the constancy of the results obtained.

TABLE I

List of endotracheal connections tested.

Right-angled:	Rowbotham
	Cobb suction
	Magill suction
Curved:	Magill nasal
	Magill oral
	Magill universal
Straight:	Forrester
	Nosworthy
	Rendell-Baker

TABLE II

Resistance of Magill nasal connectors, measured on five separate occasions.

No. of connector	Resistance in mm					Average
7	127	127	128	130	128	128
8	61	61	62	62	62	62
9	33	32	32	32	32	32
10	18	18	18	18	18	18
11	12	12	12	12	12	12
12	8	8	8	7	8	8
12A	6	6	6	6	6	6
12B	4	4	4	4	4	4

TABLE III

Minimum internal diameters of endotracheal connectors (in 64ths of an inch: 1 inch = 2.54 cm)

Number of connector:	0	1	2	3	4	5	6	6A	6B
Rowbotham		12	16	20	23				
Cobb suction			15	17	20				
Magill suction		12	14	20	24				
Magill nasal		10	12	14	16	18	20	21	23
Magill oral		10	12	14	16	18	20	21	23
Magill universal	9	12	16	20	24				
Forrester		12	16	20	24				
Nosworthy		16	18	22	26				
Rendell-Baker		11	16	18	24				

The minimum internal diameters of the connectors were measured by using high speed twist drills accurate to 1/64 inch (0.038 cm approx.) and all the connectors were new and therefore theoretically smooth inside and without any dents.

RESULTS

Table III shows the minimum internal diameters found (the Magill nasal connectors are, of course, numbered from 7 to 12B but are placed under numbers 1 to 6B for convenience). From this it can be seen that there is considerable variation in diameter between the different types of connectors, and an attempt to compare the resistances of comparable numbers would be meaningless. Figure 2 and table IV show instead a comparison of those connectors which were found to have the same diameters. Numbers 3 and 4 Forrester and 2, 3 and 4 Nosworthy connectors were found to have no resistance at all (table IV) and are therefore not shown in the figure.

DISCUSSION

It is obvious that a sharp bend will greatly increase the resistance to the flow of a gas, the extent of the increase being dependent on the sharpness of the bend. If the inner bend only is rounded, there is a drop in resistance to one fifth of the value when both bends are sharp, provided that the radius of the inner corner is not greater than 1½ pipe diameters; if the radius is larger, the resistance increases again.

Where both inner and outer corners are rounded, the resistance will be minimal. As the radius of the bend increases, the resistance drops,

TABLE IV

Internal diameters (in 64ths of an inch: 1 inch = 2.54 cm) and resistances (in mm) of endotracheal connections.

Internal diameters:	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26
Rowbotham				69				22				6			4			
Cobb suction							29		19			12						
Magill suction				71		31						10				5		
Magill nasal		128		62		32		18		12		8	6		4			
Magill oral		108		47		26		12		8		4	3		2			
Magill universal	118			42				12				4				2		
Forrester				20				5				0				0		
Nosworthy								2		0				0				0
Rendell-Baker			66					14		9						4		

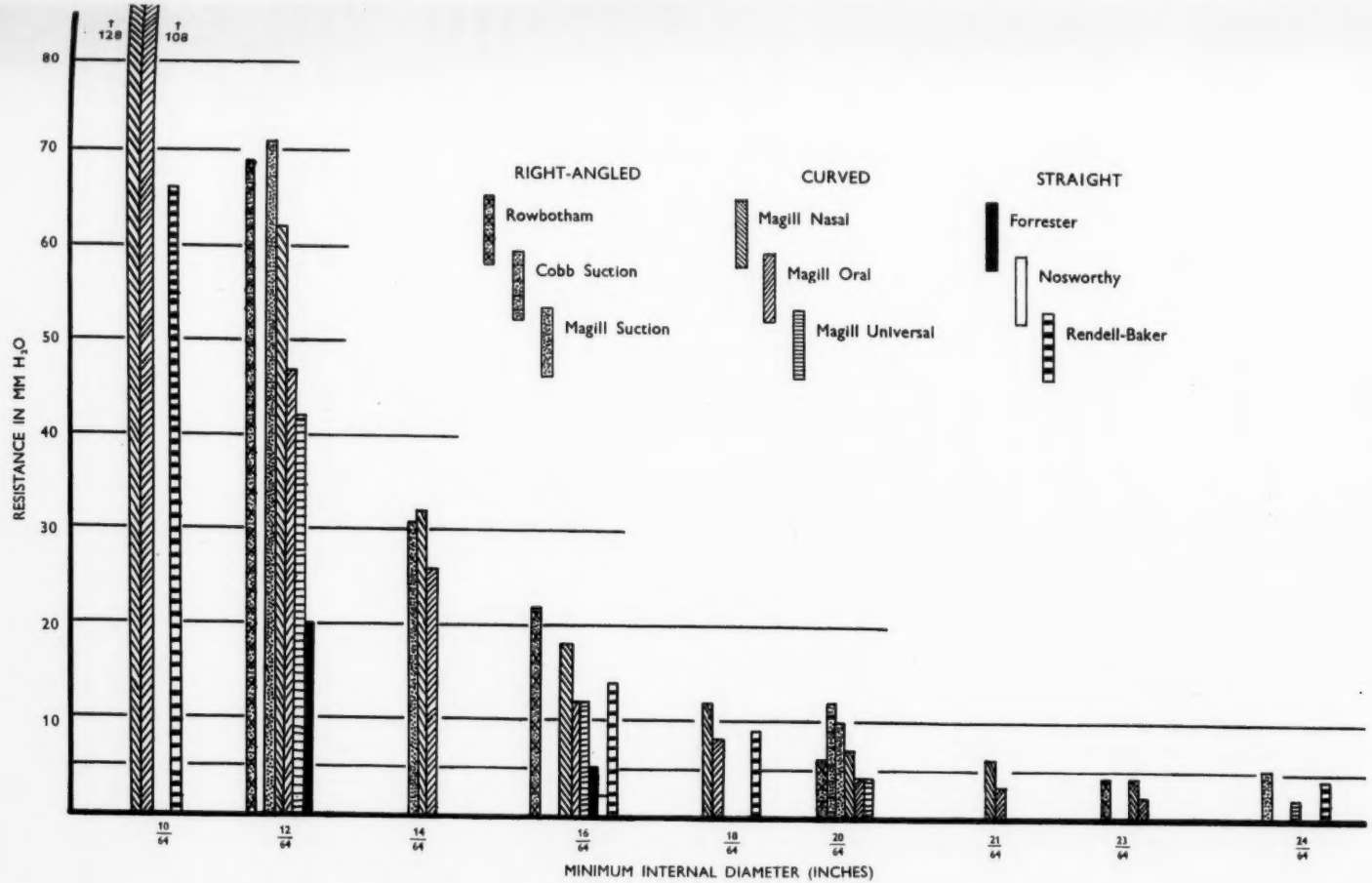

FIG. 2
Resistance of Endotracheal Connectors.

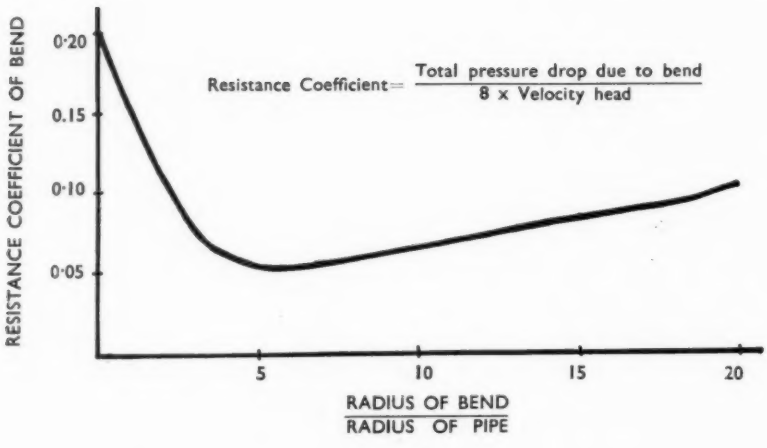

FIG. 3
The resistance of bends.

but not indefinitely (fig. 3); the minimum resistance is offered when the mean radius of the bend is six or seven times the pipe radius (Owers, 1949).

The above theoretical considerations are fully borne out by the results obtained in practice (fig. 2); for a particular diameter the resistance offered to the flow of a gas would be (from lowest to highest):

(1) Straight type of connector (such as Forrester).
(2) Angled connector with rounded corners of 90° arc (such as Magill universal).
(3) Angled connectors with rounded corners of more than a 90° arc (such as Magill nasal).
(4) Right-angled connector with sharp corners (such as Rowbotham).

It is interesting to note that both the Cobb and the Magill suction connectors have a greater resistance than a comparable diameter Rowbotham connector, from which they were both adapted. This is presumably due to the increased local turbulence set up by the blind end of the suction entry.

SUMMARY AND CONCLUSION

A comparison has been made of the resistance offered to the flow of gas by the endotracheal connectors commonly used in this country, using a flow rate which would approximate to the maximum velocity of flow reached by an anaesthetized patient breathing quietly at 8 litres per minute.

The factors responsible for producing resistance in the anaesthetic circuit are briefly discussed (in nontechnical language).

The following conclusions may be drawn from the results obtained:

(1) From the point of view of resistance, a straight type of connector should always be used if possible. Failing this, a curved connector is preferable to a right-angled one—this would appear to be contrary to the more usual practice.

(2) There is a marked difference in the internal diameters of various types of connectors, and a plea could well be made for the laying down of standard minimum internal diameters for the varying sizes. Failing such standardization, every anaesthetist should at least be aware of the difference in internal diameter, and therefore in resistance, offered by, for example, a number 1 Magill oral as compared with a number 1 Rowbotham.

(3) The ideal type of angled connector should have smooth rounded inner and outer bends forming a 90° arc, with the bend having a radius which is six or seven times that of the connector.

ACKNOWLEDGMENTS

I should like to express my gratitude to Dr. A. C. Forrester, Senior Lecturer in Anaesthetics to the University of Glasgow, for his considerable help and criticism throughout. My thanks are also due to M.I.E. Ltd., London, who kindly sent me on loan a complete new set of all the connectors tested.

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theatre. Local requirements should dictate whether it is large or small, just as they must be considered when deciding how long the patients will need to be retained. At one extreme, the recovery room is a special ward, large enough to accommodate all cases passing through the operation theatres of the hospital. It is merely a substitute, but often an essential one, for insufficient nursing staff—a place where a number of nurses highly skilled in the special problems of the postoperative period are always available and to which every patient must be transferred for several hours or days. Such an arrangement will deprive the surgical ward nurses of much of their interest in the patients. Alternatively, the recovery space may be small, sufficient for from three to six beds, but actually in the theatre block and within sight or sound of surgeon and anaesthetist. Into this room each patient can be placed until fully conscious and with a lastingly effective pulmonary ventilation—a relatively brief period of minutes rather than hours—and therefore free from the common immediate troubles of anaesthesia. When necessary, those exceptional patients who need special treatment or further observation can be kept for a far longer period, particularly at night. Competent nurses must be available, but perhaps—with a small recovery ward—they should be part of the theatre staff, who are best situated every day of the week to learn about the care of unconscious patients from those who know most about the subject. Such a system could be an advantage in a hospital with a nurses' training school, for all nurses spend some part of their training in the operating theatre, and presumably no one, for preference, wishes to remove all normal postoperative care from the supervision of the surgical ward sisters.

With good methods a return to a normal or near normal state usually quickly follows anaesthesia, but paradoxically the selective effect of some agents or techniques may persist well into the postoperative period. So long as this is the case special provision should be made for the patient's safety, and delegation of responsibility by surgeon and anaesthetist should only be countenanced when this has been accomplished.

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ANAESTHESIA AND SURGERY IN ADRENOCORTICAL INSUFFICIENCY

BY

JOHN W. DUNDEE

University of Liverpool

ALTHOUGH pathological conditions of the "suprarenal capsules" have been described over a century ago by Thomas Addison (1855), it is only within the past two decades that any real knowledge of the functions of the adrenal cortex has materialized. It is now appreciated that the integrity of the adrenal cortex is essential for survival in a major stress, such as a surgical operation (Roche et al., 1950).

The isolation of steroids from extracts of the adrenal cortex, and the synthesis of similarly active compounds have opened up new fields in the treatment of adrenal insufficiency. However, the prolonged use of such drugs themselves is not without danger, as far as anaesthesia and surgery are concerned.

This paper discusses some problems of anaesthesia related to adrenal insufficiency. These problems have become more acute as our knowledge of the function of the cortex increases, for, by the use of substitution therapy, operations, which were until recently considered to be a major hazard, are now becoming more common. It is proposed to discuss neither the physiology of the adrenal cortex, nor its regulator, the anterior pituitary gland.

CLASSIFICATION

Elrick (1950) divides adrenal insufficiency into three groups as follows:

(1) Primary hypoadrenocorticism (due to tuberculosis, neoplasms, nonspecific destruction or Waterhouse-Friderichsen syndrome).
(2) Secondary hypoadrenocorticism, due to anterior pituitary hypofunction.
(3) Surgical removal of adrenal tissue.

This classification will be adhered to as closely as possible. Under secondary hypoadrenocorticism it is necessary to add hormone induced (cortisone and a.c.t.h.) insufficiency, which has only become manifest recently since the clinical use of these hormones has become widespread.

PRIMARY ADRENAL HYPOFUNCTION

Addison's disease. Discussing this disease in 1931, Rowntree and Snell remarked "If treatment necessitates any surgical procedure the risk is prohibitive and should be assumed only after most serious consideration." Of 41 reported anaesthetics (in 37 cases), Addisonian crisis occurred in 26 instances and proved fatal in 12. (Rowntree and Snell, 1931; Katz and Mainger, 1941; Leavitt, 1945; Simpson, 1950; Dundee, 1951; Papper and Cahill, 1952; Schwartz et al., 1952; Riches, 1956). These included local, spinal and general anaesthesia.

The introduction of deoxycorticone acetate (desoxycorticosterone acetate, d.c.a., d.o.c.a.) in 1938, and more recently cortisone and similar drugs, has changed the outlook for patients with Addison's disease. Adequate substitution therapy makes them amenable to anaesthesia and major surgery. Papper and Cahill (1952) and Schwartz et al. (1952) have examined records of 23 anaesthetics in 19 cases at the Presbyterian Hospital, New York, and Peter Bent Brigham Hospital, Boston, and found that, proportionately, complications occurred as frequently in all anaesthetic groups and no particular technique was without a harmful effect. The occurrence of hypotension during or after anaesthesia (in 14 instances) was unrelated to the anaesthetic agents, but appeared to be the result of inadequate specific hormone therapy. Blood pressure fell suddenly, sometimes immediately after operation following an uneventful anaesthesia, and needed prompt treatment.

The maintenance of blood pressure seemed to be the best guide to the necessity for administra-

tion of d.o.c.a., parenteral fluids and vasopressor drugs.

Best and Taylor (1945) and Thorn (1949) advise against the use of morphine in patients with Addison's disease. Five patients were given it in the above series; three of these died, but they were not known to have the disease and all were unprepared for the stress of anaesthesia and surgery.

The author (1956) recently listed Addison's disease among the absolute contra-indications to thiopentone. This view was based on the occurrence of severe persistent hypotension following the administration of 400 mg of the drug to a patient for d.o.c.a. implant (Dundee, 1951). The action of the thiopentone also appeared to be prolonged as consciousness was not regained for 2½ hours and drowsiness persisted for a further 10 hours. This patient received no substitution therapy before operation and 10 mg morphine was given as pre-operative medication. With the advent of cortisone and other forms of substitution therapy this contra-indication becomes only a relative one, indicating the necessity for caution in the use of thiopentone.

CASE 1

Thiamylal, 150 mg, was given slowly over one minute, followed by cyclopropane and oxygen, for implantation of d.o.c.a. The patient, who had just recovered from severe Addisonian crisis, was premedicated with 75 mg cortisone and 5 mg d.o.c.a. by intramuscular injection. Blood pressure remained steady throughout and after the operation, and recovery of consciousness was prompt.

It cannot be conceived that the use of thiamylal, instead of thiopentone, was of any significance. Three of the patients reported by Schwartz et al. (1952) received thiopentone. One subject, who was not then known to have Addison's disease, was unprepared for surgery, but there were no untoward effects from the thiobarbiturate. Another patient, also unprepared, was given thiopentone and ether and died on the third postoperative day, in spite of treatment with blood, dextrose, Eschatin and phenylephrine. The third patient was anaesthetized on two occasions: without substitution therapy the b.p. fell to 70/50 mm Hg after thiopentone and ether, necessitating postponement of the operation; after treatment with adrenal extract, a.c.t.h. and dextrose the same anaesthetic caused a hypotension of 90/50 mm Hg, but the operation was completed and the patient recovered.

With regard to the use of thiopentone or deep ether anaesthesia, attention is drawn to the reductions in heart volume which were reported by McGavack (1941) in patients with Addison's disease. These changes were not restored by restoration of blood volume without adequate hormone therapy.

Hypoglycaemia must always be considered as a possible cause of delay in return of consciousness after anaesthesia in subjects with Addison's disease.

Schwartz et al. (1952) conclude from their survey that, in Addison's disease "anaesthetic management . . . is largely a matter of doing the least harm, rather than the most good. Patients respond to the stress of operation over a narrow range of compensation." They stress the importance of absolute precision in technique to avoid hypoxia, asphyxia or hypotension and emphasize that the specific chain of biochemical events leading to Addisonian crisis may be precipitated with relative ease by any of these factors. The loss of NaCl in the urine, with an increase in K^+, results in the loss of large quantities of water and depletion of the circulating blood volume. They recommend that specific treatment with cortisone (or a related compound) be given immediately once hypotension has occurred.

Since Schwartz's report was published (1952) experience has been gained in the use of glycocorticoids, and the following case report (Dr. J. E. Riding, personal communication) shows that their proper pre-operative use increases the scope of safe surgery and greatly decreases the hazards of anaesthesia in patient's with Addison's disease.

CASE 2

A woman aged 56, was first diagnosed as Addison's disease in 1953, from a history of weakness, wasting, loss of appetite, constipation, pigmentation in mouth and b.p. of 90/60 mm Hg. The result of Kepler's test was abnormal and the injection of a.c.t.h. failed to cause a 50 per cent fall in circulating eosinophils.

Over the next two years she was kept in reasonably good health with periodic d.o.c.a. implants.

In January 1956, she had a severe hypoglycaemic attack, which was not improved by d.o.c.a. Cortisone therapy was started and the patient stabilized on a daily dose of 100 mg. Her systolic blood pressure

fluctuated from 125 to 140 mg Hg over the next few months.

Six months later for removal of a parotid tumour 80 mg cortisone was given i.m. with atropine, 0.6 mg. as pre-operative medication. Anaesthesia was induced by the slow injection of 100–150 mg thiopentone followed by 50 mg suxamethonium. Oral intubation was carried out after spraying the pharynx, larynx and trachea with 4 per cent lignocaine and anaesthesia maintained at a light level with N_2O–O_2–trichloroethylene.

For a ten minute period the systolic blood pressure was lowered to 80 mm Hg, with trimetaphan (Arfonad) but returned to normal when the infusion was stopped.

Recovery from anaesthesia was prompt. The b.p. on return to the ward was 125/80 mm Hg. Cortisone therapy was continued after operation and on the morning after operation her b.p. was 120/80.

An uneventful recovery from two major thoracic operations performed under local analgesia, after adequate pretreatment with cortisone is described by Riches (1956).

It may be, perhaps, unwise to draw conclusions from the combined findings of several authors, but this is done in table I, since it illustrates the importance of adequate pre-operative preparation of the patient with cortisone and/or d.o.c.a. in decreasing the complications and mortality from anaesthesia and surgery in patients with Addison's disease. The glycocorticoids (cortisone and hydrocortisone) seem to be the drugs of choice for pre-operative administration but the synthetic mineralocortocoid, deoxycorticone acetate (d.o.c.a.) may be required in addition when the condition is severe. The additional stress of the anaesthesia and operation should be counteracted by increasing the dose of cortisone by 25 to 50 mg per day. If severe hypotension occurs it is best treated by infusion of 100 mg hydrocortisone, at a rate of about 25 mg per hour.

Waterhouse-Friderichsen syndrome. This is due to haemorrhage into the adrenal gland during septicemia, most commonly meningococcal. Faloon et al. (1950) found that patients showed the same failure of the eosinophil count to fall after adrenaline or a.c.t.h. as occurs in other forms of adrenocortical insufficiency. No details can be traced of anaesthesia or operation in patients who survived the acute episode, but management would be expected to be as for Addison's disease.

Tumours. Cecil (1933) found, in patients who died from removal of an adrenal cortical tumour, that the contralateral adrenal gland could not be found at autopsy. In Cushing's syndrome, Marquardt (1955) considers that there is likely to be atrophy of the contralateral gland or remaining tissue. This is probably due to inhibition of a.c.t.h. output by the overactive gland. This cause of adrenocortical insufficiency will be discussed with surgical removal of the adrenal for other causes.

SECONDARY HYPO-ADRENOCORTICISM

This occurs in any condition where there is hypofunction of the anterior pituitary gland, depriving the cortex of its normal stimulus of adrenocorticotropin:

Simmonds disease. Simmonds (1914) was the first to describe a clear relationship between a destructive lesion of the anterior pituitary gland and the clinical syndrome resulting from this lesion. Destruction can be brought about by a variety of pathological lesions e.g. ischaemic necrosis during abnormal delivery or the puerperium, tumours, granulomas, injury, surgical hypophysectomy, spontaneous atrophy and fibrosis.

Sheehan (1937, 1949), Sheehan and Murdock (1938), Sheehan and Summers (1949) and Cook et al. (1951) have described hypopituitarism after difficult and complicated labours. This cause of pituitary hypofunction, now known as Sheehan's syndrome, is explained by Sheehan and his col-

TABLE I

The effects of anaesthesia and surgery in 38 published and unpublished cases of Addison's disease, related to the pre-operative preparation of the patients with d.o.c.a. and/or cortisone.

Preparation	No. of cases	Anaesthesia	Hypotension during or after anaesthesia	Mortality
Nil	18	14 G.A. 4 L.A.	89%	56%
Specific hormone therapy	20	15 G.A. 5 L.A.	55%	0

leagues as follows. Normally after delivery there is a rapid involution of the pituitary from its physiologically hypertrophied state during pregnancy. The blood supply of the gland is thus suddenly reduced, and if this is complicated by circulatory collapse due to haemorrhage the blood flow may be reduced to an extremely low level. Thrombosis may thus be precipitated in the sinuses of the gland with consequent infarction and necrosis. It has been suggested by Nassar et al. (1950) that there may be a possible aetiological relationship between the administration of ergot alkaloids to exsanguinated patients and the incidence of postpartum destruction of the anterior portion of the pituitary.

Sheehan and Summers (1949) found the average weight of both adrenals in 26 cases of pituitary hypofunction was 4.7 g (2.2 to 7.8 g), the corresponding range for the normal adult being 10 to 15 g. The medulla remains almost unaffected, but the cortex is reduced to about 0.2 to 0.4 mm in thickness, instead of the normal of 1–2 mm. Investigations of cortical function discloses extremely low values or absence of urinary 17-ketosteroids and 11-oxysteroids. However, the glands will respond to a limited extent to stimulation by a.c.t.h. and adrenaline (Knowlton et al., 1950), in contrast with the complete depression of adrenal function in Addison's disease.

The thyroid is usually small and atrophic in Sheehan's syndrome, but the alterations of architectural structure are not as great as in myxœdema. The basal metabolic rate in usually low (−25 to −35).

Adrenal crises have been described in cases of hypopituitarism and Heyde (1953) reports on their treatment with a.c.t.h. and d.o.c.a. Prolonged coma is liable to occur, ushered in by masked hypotension and salt depletion (Wolff, 1950; Bloom and Wolff, 1955) and hypoglycaemic attacks are common. Hypothermia is another complication which may occur (Sheehan and Summers, 1952) and this may prolong the coma.

Israel and Conston (1952) described sudden death during Caesarian section (spinal analgesia with amethocaine-dextrose) in an unrecognized case of pituitary necrosis. This shows that these cases of pituitary hypofunction which have not been prepared by specific hormone therapy, are as liable to collapse with the stress of surgery and anaesthesia, as cases of primary adrenocortical hypofunction.

The following case report (Dr. R. J. Cumming, personal communication) describes an abnormal response to anaesthesia in a fairly typical case of Sheehan's syndrome.

Case 3

A married woman, aged 37, weight 116 lbs (53 kg) complained of always feeling cold, lack of energy, absence of hair under the arms and in the pubic region, amenorrhoea and loss of libido. Ten years previously an uneventful gestation was followed by a severe haemorrhage. The above symptoms led to the diagnosis of Simmonds disease. The patient was admitted to hospital for cystoscopy, because of dysuria and passage of dark red clots in the urine. On admission the B.P. was 130/100 mm Hg, pulse 70 mins, oral temperature 96.8°F (36°C).

The serum electrolytes pre-operatively were:

Chlorides	—	94 m.equiv/l.
Calcium	+	8.8 m.equiv/l.
Potassium	+	4.6 m.equiv/l.
Sodium	+	135 m.equiv/l.
Cholesterol		140 mg per 100 ml
Blood Sugar		68 mg per 100 ml
Blood urea		30 mg per 100 ml

X-ray of the skull revealed a small pituitary fossa, with thickened bone.

The events on the day of operation were as follows:

a.m.

10.00 Pre-operative medication of papaveretum 11 mg, scopolamine 0.2 mg.

Noon Immediately prior to anaesthesia the patient was drowsy, but responded to questioning and was co-operative. Anaesthesia was induced with 10 mg d-tubocurarine chloride, followed by thiopentone. This latter was given slowly and the patient lost consciousness after 300 mg. A further 100 mg was given, making a total dosage of 400 mg of thiopentone.
The patient became completely apnoeic and controlled respiration was carried out with nitrous oxide (6 l./min) and oxygen (2 l./min) using a semi-open circuit, with expiratory valve near the facepiece.

p.m.

12.15 Cystoscopy and retrograde ureteric catheterization completed. Patient still apnoeic.
Pulse of good volume, 65/min.
Neostigmine 2.5 mg and atropine 0.65 mg given i.v. without response.

12.30 Still apnoeic.
Niketham ide 1 ml i.v. without response.
Patient intubated.

1.00 Controlled respiration with oxygen and intermittent carbon dioxide.

1.15 Niketham ide 1 ml i.v. Respiration started. The patient coughed.
Extubated—respirations continued at the rate of 4 per minute.

p.m.
Patient deeply unconscious—pupils small and not reacting to light.
2.00 Respirations 4/min. Pulse 58/min. B.P. 110/70 mm Hg. Still unconscious.
2.45 Patient responded to stimuli.
3.00 Respirations 5/min. Pulse 60/min. Blood sugar 70 mg/100 ml. Blood urea 35 mg/100 ml. Serum alkaline phosphatase 12 AK units. Serum cholesterol 312 mg/100 ml.
4.30 Respirations, 7/min. Pulse 60/min. Patient responded to questioning.
6.00 Respirations 8/min. Pulse 70/min.
8.00 Respirations 14/min. Pulse 70/min.
Patient appeared in every way normal although she said she was very sleepy.

The following morning, the patient was fully conscious, and had no adverse after effects. The b.p. was 110/70 mm Hg with respiratory rate of 16–18 per min.

There is no doubt that this was an abnormal response to anaesthesia, regarding the aetiology of which one can only postulate.

(1) The gradual return of the respiratory rate to normal is suggestive of an overaction of the opiate, rather than the thiopentone. As far as is known, the patient had not had opiates for several years prior to this event. A mistake in dosage would have been detected earlier, since two hours elapsed between the administration of the papaveretum and the induction of anaesthesia. Nevertheless, one must consider the recommendation mentioned already by Best and Taylor (1945) and Thorn (1949) that patients with adrenocortical insufficiency should not receive opiates.

(2) Low basal metabolic rate would interfere with the metabolism of both thiopentone and papaveretum.

(3) Synergism between two drugs to each of which the patient, by reason of her complaint, proved sensitive. The enhancement by morphine of respiratory depression by thiopentone has recently been convincingly demonstrated by Helrich et al. (1956).

(4) It is unlikely that there was a markedly abnormal reponse to d-tubocurarine chloride, as slow respiration is not normally a clinical feature of partial curarization.

(5) Hypoglycaemia as a cause for prolonged coma, can be excluded on the blood sugar reading before return of consciousness.

(6) Hypothermia is also unlikely as a cause of coma, since there was no previous history of similar attacks and two isolated readings of oral temperature during the procedure were 96.8°F (36°C) and 98°F (36.9°C). The environmental temperature in the theatre was approximately 70°F (21.1°C).

(7) Hypotensive crises cannot be excluded as the cause of apnoea early on in the procedure, but even in the absence of serial blood pressure readings, this was unlikely to have persisted for long without detection. The pulse rate of 65/min. is not in keeping with a severe fall in blood pressure, although the anaesthetist commented that the pulse volume was weak after the end of the operation.

(8) Because of the clinically accurate picture of pituitary hypofunction due to Sheehan's syndrome, it can be assumed that, since replacement therapy was not given, some degree of adrenocortical insufficiency was present. This was the first major stress that the patient had encountered since her pregnancy and delivery ten years previously (which was before the onset of hypopituitarism). The response to anaesthesia must be considered to be an abnormal reaction to stress in the absence of a fully active adrenal cortex. The urinary infection may have acted as an additional stress.

Pituitary tumours. Roche et al. (1950) have drawn attention to adrenocortical insufficiency occuring in patients with pituitary tumours. They describe a patient in whom the eosinophil count only fell 15 per cent after a.c.t.h. One dose of a.c.t.h. was given prior to craniotomy, but the patient developed such severe hypotension under ether anaesthesia that the operation had to be postponed. Recovery took place after large doses of cortical extract, and six days later after continuous substitution therapy the patient withstood the same anaesthesia and surgical removal of a chromophobe adenoma satisfactorily.

Ingraham et al. (1952) state that some degree of endocrine dysfunction is probably present in nearly all patients with a craniopharyngioma (suprasellar cyst, Rathke's pouch tumours, adamantinoma, cholesteatoma, hypophyseal duct tumour) although in children it is less likely to be apparent than in adults. They review 187 operation cases with an overall mortality of 37 per cent. In cases with replacement of adrenocortical hormones there was no mortality. The mortality of unprepared adults was 41 per cent and 25 per cent in

two series of adult patients, as compared with 6 per cent in children.

The operative procedure may in itself compromise pituitary function, where this is not already too depressed, and Ingraham and Matson (1954) suggest the use of pre-operative cortisone or a.c.t.h. as a routine procedure. Ingraham et al. (1952) think that hormonal therapy might well be extended to any surgery in the parasellar region, as a prophylactic against the complications of operative trauma to the hypothalmus or pituitary gland.

Hayes (1954) describes two patients with pituitary adenomata, in whom adrenocortical insufficiency was diagnosed before operation (by the eosinophil test). Both were prepared for surgery by the administration of 100 mg cortisone daily for four days. In one patient the operation was carried out uneventfully, with a smooth post-operative course, despite the fact that the eosinophil count rose considerably during the operation. In the other patient in whom the operation was more difficult, two rises in the eosinophil count occurred and each was associated with marked hypotension from which recovery followed after adrenal cortical extract. Hayes considered the preparation of these patients to be inadequate since intramuscular deposits of cortisone, which liberate it at a fixed rate, may not rise to the increased demand during severe stress unless sufficiently large doses are used.

The following report substantiates the importance of adequate hormonal substitution therapy in such cases.

CASE 4

A fit male had an uneventful removal of a pituitary adenoma. Papaveretum 21 mg and scopolamine 0.4 mg was given as pre-operative medication. Anaesthesia was induced with 400 mg thiopentone and oral intubation carried out after 60 mg gallamine triethiodide. Maintenance was with nitrous oxide-oxygen-trichloroethylene with further increments of thiopentone to a total of 800 mg. The b.p. and pulse remained steady throughout and all blood loss was fully replaced. Consciousness returned within 20 minutes of the end of the operation.

Four hours postoperatively, the b.p. was found to be unrecordable and the pulse uncountable. The patient was unconscious with a temperature of 104°F (40°C). Oxygen was administered and the patient was sponged with ice water. Infusion of adrenaline, followed by noradrenaline was without effect on the b.p. and the patient died two hours later. Autopsy revealed no cerebral cause for the death: the adrenals were not examined.

The fatal outcome in this case is most likely to have been due to adrenal insufficiency, although this possibility was not considered at the time. Details for the pre-operative preparation with cortisone or a.c.t.h. of patients for surgery of the pituitary gland are given by Ingraham et al. (1952).

Drug Induced Adrenocortical Insufficiency.

The simulation of hyperfunction of the adrenal cortex produced directly by cortisone and similar drugs, or indirectly by a.c.t.h., is accompanied by a wide variety of physiological and metabolic changes, some desirable and others unfavourable. Among the latter are alterations in the function of the anterior pituitary gland and adrenal cortex, which maintains the ability of the body to withstand many different types of stress. The increased blood glycocorticoid level (which exogenous cortisone produces directly, and which exogenous a.c.t.h. produces by adrenal stimulation) leads to inhibition of endogenous a.c.t.h. This in turn leads to marked hypoplasia of the adrenal glands.

Cortisone and similar compounds. Adrenocortical function has been studied in 19 patients who were receiving long term cortisone therapy. In the first report, by Engleman et al. (1953), the drug had been administered for periods of 13 to 38 months, and the more recent publication (Fredell et al., 1955) reports on the same subjects after 30 to 50 months cortisone treatment. Both studies revealed suppression of adrenocortical function. It was uncertain whether the degree of suppression was proportional to the duration of treatment. The cortex was still responsive to stimulation by a.c.t.h., but the response was delayed. Thyroid activity appeared to be unaffected by the prolonged cortisone therapy in these patients, although other workers (Wolfson et al., 1950; Fredrickson et al., 1952) have produced good evidence of hypothyroidism resulting from prolonged cortisone therapy.

Solassa et al. (1953) and Bennett (1954) found a decrease in the weight of the adrenal gland at autopsy when more than 5 days cortisone therapy had been given not less than 20 days prior to the death of the patients. If the drug had been stopped

for more than 21 days before death, no significant changes were found in the adrenals. They stressed the fact that adrenocortical insufficiency may develop after as little as five days treatment with cortisone. Clinical reports (to be discussed later) suggest that adrenal insufficiency may persist, after withdrawal of the drug, for much longer than the 21 days after which the glands regained their normal weight.

There is histological evidence that cortisone-induced adrenal dysfunction is a reversible change (O'Donnell et al., 1951). One patient whose therapy had been stopped 51 days prior to death, had a zona glomerulosa of normal width and hypertrophic cells in the fascicular and reticular layers, similar to those seen after the administration of a.c.t.h.

O'Donnell et al. (1951) and Solassa et al. (1951) found that the adrenal changes found in patients treated with cortisone resemble those seen in patients who had clinical and postmortem evidence of hypopituitarism. This supports the theory that exogenous cortisone induces adrenal atrophy by suppressing the secretion of pituitary adrenocorticotropic hormone.

Adrenocorticotropic Hormone (*a.c.t.h.*).

Lewis et al. (1953) suggest that a.c.t.h. therapy is less likely to result in adrenocortical insufficiency, after its withdrawal, than is cortisone. Long term a.c.t.h. administration leads to no decrease, but even sometimes to an increase, in adrenal size, because the exogenous a.c.t.h. more than compensates for the diminished a.c.t.h. output by the anterior pituitary. However, Solassa et al. (1953) point out that it is unlikely that the use of a.c.t.h. will entirely eliminate the risk, since, like cortisone, a.c.t.h. leads to histological changes in the pituitary and endogenous adrenocorticotropic hormone output is therefore suppressed by the exogenous drug. After cessation of treatment with a.c.t.h., the adrenal cortex is fully responsive to pituitary stimulation, if the function of this latter has not been too markedly suppressed, whereas after cortisone the adrenal is partially or wholly incapable of response to pituitary stimulation.

Thorn et al. (1950) have summarized drug-induced adrenocortical insufficiency as follows—"Either preparation (cortisone and a.c.t.h.) induces anterior pituitary hypofunction owing to increased endogenous production of adrenal steroids after a.c.t.h. administration and to the administered steroid itself after cortisone. At the end of the administration of a.c.t.h., the delayed return of the hypoactive pituitary function to normal deprives the hypertrophied adrenal cortex of stimulation and leads to transient adrenal hypofunction as measured by steroid excretion. After cortisone the marked cortical atrophy accentuates temporary adrenal hypofunction."

Sudden withdrawal. Headache, nausea, vomiting, restlessness and muscle and joint pains, occurring 24 hours after sudden withdrawal of cortisone from patients previously receiving the drug over a long period, have been described by Henneman et al. (1955). Lewis et al. (1953) describes a syndrome similar to Addison's disease after sudden withdrawal of cortisone. They state that withdrawal of a.c.t.h. seldom leads to the prompt relapses in disease and the quasi-Addisonian state which may follow sudden cessation of oral cortisone therapy. This may be due to the increased responsiveness of the patients' adrenal cortex fully compensating for the lessened pituitary adrenocorticotropin output.

Anaesthesia and surgery. Lundy (1952, 1953) drew the attention of anaesthetists to the possibility that a hypofunctioning adrenal cortex (induced by cortisone therapy, and persisting after discontinuation) may be inadequate to maintain the patient through the usual stress of anaesthesia and surgery. An editorial in the *Journal of the American Medical Association* (1952) drew attention to this hazard, as have Wood-Smith and Payne (1955) in this country. Some of the published case reports which evoked these warnings are summarized below.

A patient who underwent major surgery after receiving cortisone for a period of eight months, died of immediate postoperative "shock", in spite of normally adequate therapy (Fraser et al., 1952). Spinal analgesia and thiopentone were employed and the pre-operative b.p. of 140/80 mm Hg did not fall below 118/80 mm Hg during operation, with pulse rate varying between 72 and 80 per minute.

Autopsy: Marked bilateral adrenal atrophy.

Solassa et al. (1953) describe two postoperative deaths (following a gastrectomy and bunionectomy) in patients who had been previously treated with cortisone.

Lewis et al. (1953) reported a fatality in the imme-

diate postoperative period in a patient who received cortisone (62.5 to 100 mg) daily for a period of 5 months (total dose, 8.5 g) for rheumatoid arthritis. Operation was a corrective tendon lengthening, lasting 2½ hours. Anaesthesia was with thiopentone-nitrous oxide-oxygen, during which b.p. was 120–110/80–70 mm Hg, and pulse rate was 80–90/min throughout.

On return from surgery the b.p. dropped to 80/60 mm Hg. One and a half hours postoperatively the patient was restless, pulse thready, rapid and uncountable with unrecordable b.p. Oxygen and blood transfusion produced some improvement. Two hours postoperatively, the pulse rate was 164/min, respiratory rate 48/min; hyperpyrexia had occurred and the patient was still restless.

Cheyne-Stokes respiration developed 5½ hours after operation and the patient died 15 minutes later.

Autopsy: Both adrenals were smaller than normal. Atrophy of both cortex and medulla. Pituitary normal, save for slight hyperaemia.

The authors at first thought that this was a case of Waterhouse-Friderichsen syndrome, but it proved to be more than a simple haemorrhagic lesion. The disappearance of medullary tissue may have been an artefact.

The following case reported by Harnagel and Kramer (1955) is instructive, since prior to the incident described the patient had undergone seven identical procedures, before the onset of cortisone therapy, without incident.

Cortisone, 1.9 g, had been given over one month for rheumatic spondilitis with peripheral joint involvement. Thiopentone (dose not recorded) was given for a manipulation, which lasted about one minute. The recovery was somewhat slow, as the result of which the patient missed the evening dose of cortisone.

Twelve hours after operation the patient was deeply comatosed, cyanosed, sweating, b.p. unrecordable, pulse rate 140/min, eosinophils 240/cu. mm.

Treatment was with l-noradrenaline infusion in 5 per cent dextrose, containing 80 units a.c.t.h. per litre. Approximately 80 units were given per 24 hours. Adrenal cortical extract (Eschatin) was also given intravenously and cortisone administered rectally, then by i.m. injection. The patient remained moribund and hyperpyrexial for 24 hours, pulse 140–160/min. Twitching of muscles occurred, resembling decerebrate rigidity, and this was not affected by calcium gluconate.

Improvement began on the second postoperative day, the b.p. being 90/70 mm Hg.

The patient gradually regained consciousness and there were no untoward sequelae.

This patient had received no cortisone for 18 hours before operation, and for 30 hours before the onset of shock. The normal eosinophil count after surgery and after a.c.t.h. (Roche et al., 1950) is indicative of adrenal hypofunction. The muscle twitchings were attributed by the authors to be due to cerebral hypoxia. They point out the hazards of pre-operative preparation with oral cortisone, after which the peak blood concentration is attained in 4 hours, the drug being completely dissipated in 12 hours. The use of the intramuscular route provides a depot, from which the cortisone is gradually released into the circulation. The following cases further illustrate the hazards that are attendant on the administration of cortisone, and for some time after cessation of treatment.

Case 5

A 27-year-old female medical student who appeared to be in excellent health, had dislocated her shoulder about four hours prior to anaesthesia. Atropine 0.6 mg was given intravenously, followed five minutes later by the very rapid administration of 500 mg of 5 per cent buthalitone sodium. This produced the desired relaxation, and the dislocation was reduced without difficulty and a sling applied. The whole procedure was completed in less than one minute.

The rapid return of consciousness expected with this anaesthetic technique did not occur. Ten minutes after the buthalitone, the patient was still sound asleep, respirations were fast and shallow and there was slight cyanosis of the extremities. Silent aspiration of gastric secretions was suspected, but auscultation revealed good air entry on both sides of the chest. Inhalation of oxygen was commenced, but the cyanosis persisted. Controlled respiration was instituted five minutes later, with lessening of the cyanosis. The contents of all ampoules were checked to exclude the possibility of a relaxant being confused with atropine.

Twenty minutes after the anaesthetic, the b.p. was recorded for the first time and found to be 60/40 mm Hg with a pulse rate of 140/min. The patient was placed in 20° head down position and 2.5 mg methoxamine given intravenously and 5 mg by intramuscular injection. Within 5 minutes the pulse rate had dropped to 70/min, the patient opened her eyes, although the b.p. had only risen to 90/60 mm Hg. Oxygen inhalation was continued, but the respiratory volume was now adequate. Infusion of 5 per cent glucose in normal saline was started, so as to be available should the administration of l-noradrenaline be required.

The b.p. rose slowly over the next half hour, and was 110/75 mm Hg with pulse rate of 60/min, one hour after the induction. The patient was still drowsy. Half a litre of the fluid (25 g glucose and 4.5 g NaCl) had been run in quickly and the infusion was discontinued.

Consciousness had returned to normal and the patient was walking around, anxious to leave hospital, six hours later. She was retained overnight and in the morning e.c.g., serum K^+, Na^+ and Cl^- and blood urea levels were all within the range of normality.

There was no previous history of collapse following anaesthesia, although appendicectomy had been performed two years previously (under spinal anaesthesia) and a cervical dilatation for dysmenorrhoea was carried out (under thiopentone-cyclopropane anaesthesia) about 8 years previously. Her last illness was

seven weeks before the dislocation when arthralgia of unknown aetiology responded to cortisone therapy. Until 28 days before the above incident she had been taking 12.5 mg cortisone daily for one week, preceeded by 25 mg daily for a further week. The total dose given was not known, but she said that large doses were given to her at the beginning of the treatment.

The diagnosis of cortisone induced adrenocortical insufficiency in this patient is based entirely on the history, and on the similarity of the post-operative course to that of the cases already described. In the next case, the presence of drug induced cortical insufficiency is more certain.

Case 6

A woman, aged 30, had been on oral cortisone therapy for almost two years, the daily maintenance dose being 25 mg in two divided doses. General health was good. Operation was uterine curettage.

The morning dose of 12.5 mg cortisone was taken at 7.0 a.m.; pre-operative medication of quinalbarbitone 100 mg and hyoscine 0.4 mg was given i.m. at 1.0 p.m. and anaesthesia induced with thiopentone at 2.15 p.m. Maintenance of anaesthesia, which was with intermittent thiopentone-nitrous oxide-oxygen, was uneventful. The b.p. on leaving the theatre at 2.50 p.m. was at the pre-operative level of 115/70 mm Hg, but the pulse rate had increased from 84 to 116 per minute. As far as could be ascertained the return of consciousness was not delayed, and the condition of the patient on return to the ward did not cause any concern. About 4 p.m. the patient was found to be moribund with an uncountable pulse rate and unrecordable blood pressure. She was barely conscious. Respirations were fast and shallow.

Two possible diagnoses were considered (*a*) rupture of the uterus, and (*b*) acute adrenocortical insufficiency. Treatment: immediate i.m. injection of 5 ml cortical extract (Eschatin). Blood transfusion and infusion of phenylephrine were started. One pint of blood, given quickly had no effect on the blood pressure and as phenylephrine was also without value, l-noradrenaline was substituted after one hour. The blood transfusion was replaced by 5 per cent dextrose containing 75 mg cortisone per 500 ml. The patient gradually lapsed into coma, and at 6.0 p.m. since the noradrenaline was ineffective in raising blood pressure, it was replaced by dextran. Two further doses of Eschatin had been given. Oxygen therapy was also started.

At 9.0 p.m. about 125 mg cortisone had been infused and preparations were being made for laparotomy, when l-noradrenaline was restarted. This raised the systolic blood pressure to 60 mm Hg. In view of this improvement, surgical intervention was postponed. Twelve hours after operation the b.p. could be maintained at 70/40 mm Hg by a slow infusion of l-noradrenaline. The patient was still unconscious and improvement instead of expected deterioration in her condition led to cancellation of the laparotomy. By now one litre of dextrose (150 mg cortisone) had been given and this infusion was stopped and 25 mg cortisone acetate given i.m.

On the morning after operation the patient was conscious but drowsy and slightly restless. The b.p. was 90/50 mm Hg without l-noradrenaline. The respirations were still fast and shallow, and the breath sounds were absent at the base of one lung. Oral temperature was 38.5°C (101.3°F). The improvement was not maintained, respiratory distress increased and the patient again lapsed into coma. A slow 5 per cent dextrose in normal saline infusion containing 100 mg hydrocortisone was started and a further 25 mg cortisone given i.m. Massive doses of antibiotics were given parenterally.

Tracheobronchial toilet was performed 20 hours after operation and much frothy mucous removed. This produced an almost immediate improvement and by the evening the patient was again conscious, the b.p. was 100/70 mm Hg (without l-noradrenaline) and all intravenous therapy was stopped. In spite of the prompt treatment enormous doses of cortisone and similar drugs were required during the first 24 hours after operation (cortisone 150 mg i.v., 50 mg i.m.; hydrocortisone 100 mg i.v.; Eschatin 15 ml i.m.).

Roche et al. (1950) point out that hypokalaemia and hypochloraemia which accompanies the administration of excess cortisone can cause muscular weakness and paralysis. It is a matter of speculation whether this played any part in the pulmonary collapse in this patient.

The failure of blood pressure response to phenylephrine and the early poor response to l-noradrenaline are very different from the effects of methoxamine in case 5. It is unlikely that this points to a preference for the latter pressor amine, as the duration and intensity of cortisone therapy and the degree of vasomotor collapse were much greater in the second patient.

Case 7

Male aged 74, weight 150 lbs (68 kg). Admitted to hospital with acute intestinal obstruction. Four months previously laparotomy was performed for perforated peptic ulcer, which was found to be due to an inoperable carcinoma of the stomach. For some unknown reason, the patient had been given 25 mg cortisone daily since his discharge from hospital. His general condition was fairly good until two days before admission to hospital when he began to vomit. He had not taken the cortisone during these two days.

The possibility of adrenocortical insufficiency with its attendant dangers was fully appreciated before induction of anaesthesia. Pre-operative medication was with cortisone 150 mg i.m., d.o.c.a. 5 mg i.m., and atropine 0.4 mg. The subsequent course of anaesthesia and the immediate postoperative period are shown in figure 1.

Two severe blood pressure falls occurred during the operation and the only evidence that they may have been partly due to adrenocortical insufficiency is the prompt response to intravenous hydrocortisone. This patient died on the 13th postoperative day from generalized peritonitis arising from his surgical condi-

tion and atrophy of the cortex of both adrenal glands was found at autopsy.

Case 7 shows the value of a pre-operative appreciation of the possibility of adrenocortical insufficiency in patients who have been or are still receiving cortisone or a.c.t.h. therapy. What the course of events in this patient would have been in the absence of the pre-operative administration of cortisone is a matter for speculation, but on the basis of previous reports, the smooth postoperative course would not have been expected.

While the immediate recognition of post-operative collapse due to quasi-Addisonian crisis is obviously important and sometimes lifesaving (as in two of the above cases), it is vital that the possibility of adrenocortical insufficiency be appreciated pre-operatively and that substitution therapy be included in the pre-operative medication.

Experience shows that it seems to be easier to prevent a collapse than treat already established hypotension. The severity of the operation does not seem to be important as any operative procedure appears to be a sufficient stress to induce hypotension. Whether this would be caused by anaesthesia alone is not known. Roche et al. (1950)

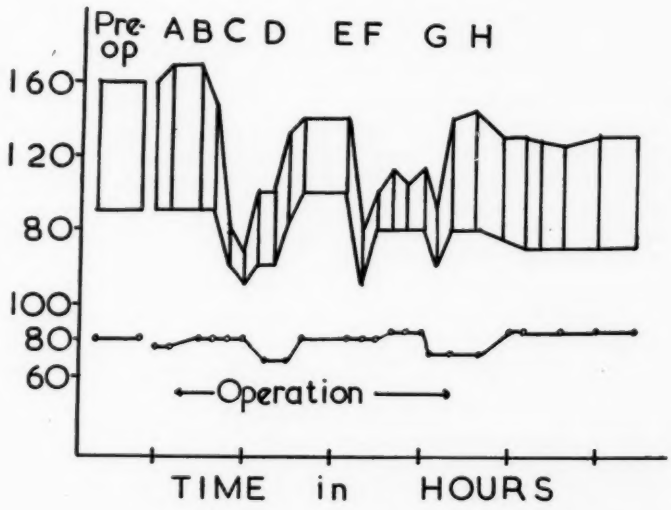

FIG. 1

The course of anaesthesia and operation in case 7.

A Oral intubation under topical (10 per cent cocaine) anaesthesia. Induction with 150 mg 2.5 per cent thiopentone, followed by cyclopropane and oxygen. Suxamethonium 0.2 per cent infusion started.
B Slow blood drip started.
C Exploring abdomen: Blood pumped in fast. 20 mg hydrocortisone acetate i.v.
D Operation stopped for 10 minutes.
E 1,000 ml blood given: Saline infusion started containing 100 mg hydrocortisone acetate.
F Exploring abdomen.
G Closing abdomen: suxamethonium stopped.
H Respirations spontaneous: extubated; skin warm and dry, colour satisfactory; responds to name.

Postoperatively: Cortisone 50 mg six hourly I.M. for 24 hours; 25 mg six hourly for next two days. Parenteral fluids continued for 48 hours. Gradually decrease in cortisone dosage until 25 mg given b.i.d.

found that patients failed to show a fall in eosinophils after thiopentone anaesthesia alone. They thought that anaesthesia might block a normal pituitary-cortex response and a maximum stress may be needed to break through this inhibition. This probably depends on the method of administration of the thiopentone, as the severe hypotension which follows its rapid injection can obviously act as a stress in itself. In support of this view is the immediate collapse after its rapid injection in a case of Addison's disease (Dundee, 1951) and a similar occurrence following the rapid administration of another thiobarbiturate (buthalitone) in case 1. In the two other cases of Addison's disease described previously and in cases 2 and 3, the drug was administered slowly. It is not possible to confirm or refute this hypothesis on the data given by the authors in the cases of drug induced cortical insufficiency described above.

Pender (1954) discusses the anaesthetic management of cases of induced adrenocortical insufficiency in which the condition was recognized before induction. He advises substitution of pethidine for morphine, and caution in the use of respiratory depressant drugs, unless reliable facilities are available for the maintenance of an adequate tidal volume. It would also seem advisable to avoid the drugs which cause severe falls in blood pressure such as deep ether or rapidly injected thiopentone.

Since patients with other types of adrenocortical insufficiency, if properly prepared for operation, can withstand controlled hypotension without ill effects, there is no reason to believe that, with the similar preparation, the patients in this group will behave differently. Again, it must be stressed that the first step in treatment is awareness of possible adrenocortical insufficiency in patients receiving cortisone or a.c.t.h., or who have received either drug within the past 12–18 months.

Solassa et al. (1953) comments that many thousands of patients must have been operated on after cortisone without ill effects, and considers that the risk involved is not very great. It may be of significance that the first warnings of this danger came from the Mayo Clinic (Lundy, 1952, 1953; Patrick et al., 1952; Pender, 1954) where the treatment of rheumatoid arthritis with a.c.t.h. and cortisone by Hench et al. was described as early as 1949, and where the deaths reported by Solassa et al. occurred. In this country, cortisone only became generally available on December 5, 1955, and, as yet, the percentage of patients who are receiving, or have received, the drug is unlikely to be as great as in the United States. Its use may increase in Britain and since there is no simple method of predetermining which patients are liable to collapse, all cases should be questioned before operation as to previous cortisone therapy.

Many recommendations have been made on the pre- and postoperative dosage of cortisone in patients with adrenocortical insufficiency (Elrick, 1950; Huggins and Bergenstal, 1951; Ingraham et al., 1952; Lewis et al., 1953; Romagnoli, 1955). The more recent of these should be consulted for details. As a rough guide, 100–150 mg cortisone is given daily on the two days before operation and the same dose repeated by intramuscular injection one hour before the induction of anaesthesia. After operation 25–50 mg is given parenterally every four to six hours, and the frequency of administration is gradually decreased over a period of 7 to 10 days, until a satisfactory maintenance dose is obtained, if such is necessary.

SURGICAL REMOVAL OF ADRENAL TISSUE

Bilateral adrenalectomy for nonmalignant tumours of the adrenals is becoming more widely practised for advanced carcinoma of the breast or prostate and in some cases of severe hypertension. In these patients it is obvious that adrenocortical insufficiency may occur and replacement therapy is administered as a routine (Hollander et al., 1952; Galante and McCorkle, 1955; Govearts et al., 1955; Cade, 1956; Latham, 1956). Despite the fact that they may have extensive metastases or cardiovascular disease, perhaps because of this pre-operative preparation, the risk of hypotension occurring in them during or after operation is less than in patients who are not so seriously ill (as in previous group), but in whom adrenocortical dysfunction has not been diagnosed before operation. Latham (1956) advises the administration of cortisone before removal of the first adrenal in patients with malignant disease, in case the second gland

may be replaced by carcinomatous tissue. Occlusion of the veins of the second gland, with resultant diminution of output of catechol amines, frequently results in an abrupt fall in blood pressure, which can be corrected by infusion of l-noradrenaline.

Collier (1955) has described the use of controlled hypotension (with hexamethonium) in an adrenalectomized subject. Cortisone 150 mg was given by intramuscular injection two hours before induction of anaesthesia, the course of which appeared to be what one would expect in a normal subject. The blood pressure rose from 70/50 to 80/50 mm Hg when the table was levelled, but the return to normal was slightly delayed and infusions of blood and dextran were given. Cortisone therapy was started two hours after operation, and almost certainly prevented postoperative hypotension. In the light of the previous discussion, it is worth recording that this patient received 10 mg morphine as pre-operative medication, and the same dose was repeated one hour and six hours after operation, without any detectable effect on the blood pressure.

Attention has already been drawn to the atrophy of one adrenal cortex that frequently accompanies hyperactivity of the other gland. The management of patients with hypercorticism may be difficult as the patient is plunged from hypercortical activity to adrenocortical insufficiency without time to allow opportunity for adjustment (Elrick, 1950). Walters and Kepler (1938) reported 50 per cent mortality from removal of 40 adrenal cortical tumours, before the introduction of cortisone. Perkoff et al. (1955) found that postoperative hypotension was more common after operations for Cushing's syndrome than after adrenalectomy, for indications are that the gland itself is not affected. In place of the 100 mg of cortisone which is given 48, 24 and 1 hours before adrenalectomy, Latham (1956) recommends double this dose in patients with Cushing's syndrome. Removal of a hyperfunctioning adrenal cortex may also be carried out in patients with female pseudohermaphroditism (adrenal virilism) and in the patient the use of large doses of cortisone is recommended before and after operation (Jones and Jones, 1954).

UNRECOGNIZED ADRENOCORTICAL INSUFFICIENCY

There is a growing accumulation of clinical data which suggests that in many cases, not fitting into any of the above categories, the appearance of intractable hypotension (not accounted for by blood loss, posture etc.) during anaesthesia and surgery may be a manifestation of failure of the adrenal cortex (Galante et al., 1954; Hayes, 1954). Howland et al. (1956) describe 7 cases in support of this view and, in addition, suggest that other signs such as respiratory depression or failure to react after anaesthesia may be part of the same syndrome. Their patients were mostly chronically ill and in poor general condition before operation. In all cases the response to intravenous hydrocortisone was rapid and sustained.

This new concept of intractable hypotension, based on the beneficial therapeutic effects of intravenous hydrocortisone (100 mg in 500 ml 5 per cent dextrose), is worthy of serious consideration, in view of the present unsatisfactory methods of treatment of so called "irreversible shock". Although the following case report is complicated by the use of hypothermia, it is very suggestive of undiagnosed adrenocortical insufficiency.

CASE 8

A woman, aged 62, had complained of unsteadiness of gait for three years. Her general condition was fair, and although she had mitral stenosis for many years, her exercise tolerance was good.

Premedication was with pethidine 50 mg and chlorpromazine 50 mg, given by deep i.m. injection one and a quarter hours before induction of anaesthesia. On arriving in the anaesthetic room, she was sleepy but could be roused quite easily.

Anaesthesia was induced with thiopentone and continued with nitrous oxide and oxygen. Hypothermia was induced according to the technique described by Burrows et al. (1956). The subsequent course of anaesthesia is shown in figure 2. Operation was cerebellar craniotomy, with removal of a tumour from the cerebellar-pontine angle.

The comparatively sudden fall in blood pressure towards the end of operation, which was not due to operative intervention or blood loss, and its failure to improve with blood transfusion, methoxamine or l-noradrenaline, presented a problem which was solved by the intravenous administration of hydrocortisone.

SUMMARY

The conditions in which adrenocortical insufficiency may be found are discussed. The hazards

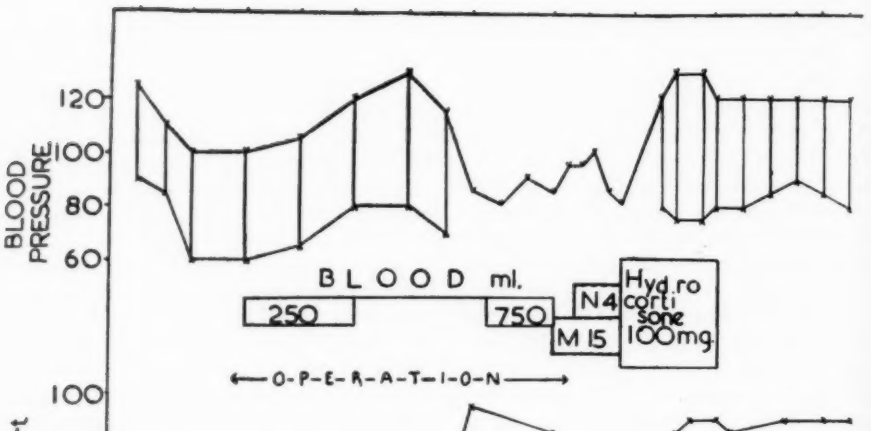

FIG. 2

The course of anaesthesia and surgery in case 8.
M 15 = methoxamine 15 mg.
N 4 = l-noradrenaline 4 mg.

of anaesthesia and operation in these cases in the absence of suitable hormonal replacement are described.

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CORRESPONDENCE

THIOPENTONE IN DYSTROPHIA MYOTONIA

Sir,—I was interested in the article on the above subject by Drs. Bourke and Zuck (*Brit. J. Anaesth.* (1957), **29**, 35) as I recently had to deal with a patient suffering from this disease during a hospital list.

An ovarian cystectomy was scheduled for a woman of thirty who had the typical facies of dystrophia myotonia with marked wasting of the sternomastoid muscles. She had a weak grip but had difficulty in relaxing it. She did not have cataract or baldness and was of average intelligence. As she was extremely apprehensive, she was given the standard premedication of pethidine 100 mg and scopolamine 1/150 grain. She arrived in the anaesthetic room with just the desired amount of sedation. Being forewarned by Dr. Dundee's description of three cases in his recent book, I started very gingerly with 2.5 per cent thiopentone. When 100 mg had been injected, the patient was deeply unconscious and apnoeic. An orotracheal tube was passed without difficulty and controlled respiration started with a 50 per cent mixture of nitrous oxide and oxygen with a trace of added trichlorethylene. When the operation started, the abdominal muscles tightened up although spontaneous respiration was still absent and divided doses of tubocurarine chloride were given up to a total of 10 mg. Relaxation was then excellent and lasted throughout the operation which took about an hour. Spontaneous breathing began in about 40 minutes and was adequate by the time the patient was returned to bed. Extubation produced coughing and recovery was normal.

It seems to me most important that anaesthetists generally should be aware of the extreme sensitivity of these patients to thiopentone or disasters are almost certain to occur.

C. LANGTON HEWER

Brit. J. Anaesth. (1957), **29**, 181

THE USE OF THE MODIFIED BEAVER RESPIRATOR

BY

ELSIE JAQUES

St. James's Hospital, Leeds

THE problem of anaesthetizing a patient with some degree of "fixed chest", due to chronic bronchitis and emphysema, must arise frequently. The following history illustrates such a case, where it was necessary to control the respiration and where the usual method, i.e. by intermittent positive pressure by manual compression of the rebreathing bag failed.

CASE HISTORY

Male patient aged 55 years, admitted 2/8/56 with a long history of duodenal ulceration and a recent, severe exacerbation. *C/O*: Pain and vomiting. No bleeding. *O/E*: Tall, fairly muscular, but of spare build, rather nervous. *CVS*: *Pulse* 80, regular. *B.P.*: 175/100 mm Hg. *H.S.*: Normal. No bruits. *Chest*: No cough. Movement poor. No added sounds. *X-ray*: "Chronic bronchitis and emphysema".

7/8/56. *Operation* proposed, partial gastrectomy.

9.30 a.m. *Premedication*: Paperveratum 21.6 mg, scopolamine 0.432 mg.

10.30 a.m. *Induction*: Pethidine 50 mg diluted in water; thiopentone 700 mg (5 per cent solution: d-tubocurarine 20 mg.

Intubated with cuffed No. 11 Magill orotracheal tube. The patient coughed after intubation, and then breathed deeply of the nitrous oxide/oxygen mixture. He was then wheeled into theatre and connected to a closed circuit with a CO_2 absorber and maintained on N_2O, 1 litre and O_2, 500 ml.

Assisted respiration, proceeding to controlled respiration, was instituted as the respiratory excursion diminished and then failed, respectively. Assisted and controlled respiration, by manual compression of the rebreathing bag, was found to be difficult. At no time was there any rebound into the bag, due to loss of pulmonary elastic tissue. The pulse became weaker as the respiratory muscles failed (fig. 1).

10.35 a.m. Respiratory movements ceased. The pulse was impalpable, and B.P. fell to zero. The operation was suspended.. The nitrous oxide was turned off. The soda lime was cut out of the circuit, and respiration controlled with pure O_2.

10.35–10.40 a.m. I.V. 5 per cent dextrose in water infusion commenced. B.P. 60/? mm Hg. Pulse, 50/min. The table was put in the head down tilt, but this did not improve the B.P.

The chest became more and more difficult to inflate by the above method and by 10.50 a.m. it was virtually impossible—the patient became cyanosed even though given pure O_2.

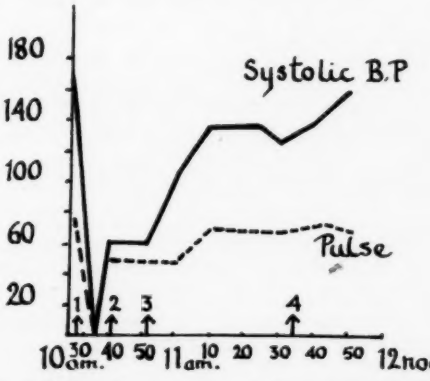
The Beaver respirator with Waters canister, and modified to give a negative intrathoracic pressure, was then connected. Within seconds the patient's colour improved and the B.P. rose to 90/? mm Hg. The colour remained good even when nitrous oxide was re-introduced in the previous proportion.

11.0 a.m. B.P. 100/? mm Hg. Pulse 70/min. The operation was continued but modified to gastroenterostomy. The B.P. continued to rise and remained steady between 130 and 145 mm Hg systolic.

11.35 a.m. d-Tubocurarine 5 mg and thiopentone 100 mg given prior to closing peritoneum.

11.50 a.m. Operation finished. CO_2 absorber was removed from the circuit. The respiration commenced spontaneously after giving CO_2 for half a minute or so. The respirator was disconnected. The patient maintained his good colour while breathing air. Atropine 1.296 mg and neostigmine 2.5 mg was given as a precaution, however.

Post Op. Sputum +; otherwise satisfactory.



1. Pethidine 50 mg
   Thiopentone 700 mg
   d-Tubocurarine 20 mg.
2. I.V. 5% Dextrose in water
3. Beaver respirator with Waters canister.
4. Thiopentone 0.1 g
   d-Tubocurarine 5 mg.

FIG. 1

In this case, the primary effect of intermittent positive pressure, was on the respiratory system. The emphysema was associated with loss of pulmonary elastic tissue and as a result, the alveoli, while they could be distended more and more by the gas flow up to a certain point, could not collapse against the positive pressure of the gases.

Respiratory exchange was interfered with and even though pure O_2 was given, if it reached the alveolar membrane at all, it would be admixed with the gases already distending the alveoli.

The secondary effect of this method was on the circulation, and followed quickly.

The absence of a negative respiratory phase presumably decreased the venous return and hence the cardiac output and B.P.

The negative phase, given by the modified Beaver respirator, reversed these untoward effects completely and without it, I am sure this patient would have died.

CORRESPONDENCE

POTASSIUM DEPLETION AND THE CENTRAL ACTION OF CURARE

Sir,—I feel that the following case history is worth reporting in view of the interesting and important articles on neostigmine resistant curarization (Hunter, 1956) and on potassium depletion and the central action of curare (Foster, 1956).

A man of 67 years was admitted to hospital with a five-weeks history of increasing dysphagia and retrosternal pain; for the last fortnight prior to admission he had only been able to ingest fluids. He had lost about a stone in weight over the past three months. His clinical condition, apart from evident weight loss, was good; the cardiovascular and respiratory systems showed no abnormality. His Hb was 80 per cent but the w.b.c. and e.s.r. were both raised. A barium swallow showed gross distortion of the lower third of the oesophagus. Biochemical investigation gave the following results:

Blood urea = 36 mg/100 ml.
Blood plasma chloride = 97 m.equiv/litre (= 568 mg/100 ml).
Blood plasma bicarbonate = 22 m.equiv/litre (= 50 vols./100 ml).
Blood serum sodium = 133 m.equiv/litre (= 305 mg/100 ml).
Blood serum potassium = 5.7 m.equiv/litre (= 22.4 mg/100 ml).

Oesophagoscopy and bronchoscopy were carried out under the following anaesthetic. Premedication: morphia 10 mg and atropine 0.65 mg. Induction: thiopentone 400 mg and suxamethonium 50 mg. A cuffed Magill tube was passed and gallamine 120 mg was given as soon as respiration had been re-established. A large fungating growth was found in the lower third of the oesophagus, which proved to be a carcinoma when sectioned, but bronchoscopy showed no abnormality. Respiratory movements were returning towards the end of this procedure and atropine 0.65 mg and neostigmine 2.5 mg were given. Full muscle tone and respiratory movement became established in the expected time and the patient was returned to the ward awake and in a normal state of muscular activity.

One week later an oesophagectomy was performed via a left thoracotomy incision. In the interval between operations the patient was given a high protein fluid diet, containing an average of 3.5 grams of potassium daily. Premedication was as before and anaesthesia was induced with pethidine 20 mg, thiopentone 450 mg and suxamethonium 100 mg. A cuffed Magill tube was passed and anaesthesia was continued with a 50 per cent mixture of nitrous oxide and oxygen. On the return of normal respiration 25 mg of d-tubocurarine was given and a further 10 mg some 30 minutes later. This was all the relaxant needed for the operation which lasted four hours. During the operation the patient's condition caused no anxiety. His colour was good and his B.P. remained at 90–100 mm Hg systolic except for a short fall to 60 mm Hg when the growth, which was extensive, was being mobilized. Blood loss was not excessive and 2½ pints (1.4 litres) of blood were given during the operation, the third pint (0.6 litre) being completed after return to the ward. A sound anastomosis was obtained which showed no evidence of leakage at autopsy.

At the end of the operation some respiratory movement, though quite inadequate, was present and atropine 0.65 mg followed by neostigmine 2.5 m.g. in divided doses was given. This produced no response and 15 minutes later the same doses were repeated, again with no effect. Half an hour later the same doses were again repeated and again there was no response. Inflation with oxygen was continued and blood was taken for biochemical analysis; this gave the following results:

Blood urea=50 mg/100 ml.
Blood plasma chloride=96 m.equiv/litre (=560mg/100 ml).
Blood plasma bicarbonate=18 m. equiv/litre (=40 vols/100 ml).
Blood serum potassium=5.9 m.equiv/litre (=23 mg/100 ml).
Blood serum sodium=138 m.equiv./litre (=316 mg/100 ml).

Clinically at this time the lungs showed good air entry and the underwater seal drain connected to the left pleural cavity was swinging satisfactorily. The

[Continued on page 186

Brit. J. Anaesth. (1957), **29**, 183

MODIFIED BEAVER RESPIRATOR

BY

GEOFFREY B. BURCHELL

Leeds "A" and "B" Hospital Groups

A SIMPLE modification to the well known Beaver Respirator is described below. This introduces a negative phase into the cycle. With the exception of a simple ring adapter all standard parts were used throughout, although certain junctions had to be filed down to fit.

The inlet valve was removed and fresh gases introduced at the patient's end (fig. 1H), utilizing a standard Waters canister (fig. 1G) and connection. The rebreathing bag of the Waters canister was removed and replaced by a length of corrugated tubing (D) connected to the mount (E) bearing the manometer tube. This manometer mount was connected by the specially made ring adapter (F) to the end of the Waters canister.

The other end of the corrugated tube (D) was connected to the patient's port of the inspiratory–expiratory valve (C). The machine port of valve (C) was connected by the short length of corrugated tubing (B) to the outlet of the machine (A).

The outlet port of valve (C) was connected by a rebreathing bag mount (I) to the machine port of a second inspiratory-expiratory valve (K), utilizing the spare valve supplied with the machine. The patient's port of valve (K) was connected by a short length of corrugated tubing (L) to the inlet mount (M) of machine. The outlet port of valve (K) was blocked with a rubber bung. A one gallon rebreathing bag (J) was attached to the bag mount (I).

The manometer was changed in position to be as near to the patient as possible. Although at the rear of the soda lime canister, the manometer is connected by nondistensible metal parts to the endotracheal tube—a Bullough's endotracheal connection being employed. In this position it will give a relatively true reading of the intratracheal pressures. The photograph (fig. 2) shows the complete arrangement.

WORKING OF THE MACHINE

The stroke volume, speed and positive pressure controls remain and work as before.

During expiration the initial recoil from the lungs is accommodated by the rebreathing bag (J). As the bellows expand the bag is emptied, then the bellows suck gases from the lungs and lower the pressure. The degree of negative pressure depends on the relationship between the amount of gases blown off during inspiration and the flow rate of new gases.

In the inspiratory phase a certain amount of gases escape from the pressure control valve. If this amount lost exceeds that which flows into the circuit, a negative pressure must be formed when the bellows reach maximum volume. The amount of negative pressure is thus controlled by altering the flow rate of incoming gases; an increase in flow rate reduces the negative pressure, a reduction in flow rate increases negative pressure.

A flow rate of 0.5 to 2 litres usually provides adequate negative pressure. A negative pressure of 15 cm of water may be obtained. The return from positive peak pressure to zero is rapid, from negative to zero is slow, thus profoundly lowering the mean pressure. The path of inspiration is shown by the continuous line in figure 1, and the path in expiration is shown by the dotted line.

It was decided to compare the intrathoracic pressure of the original and adapted machine. The machine was used on the same patient with a pressure swing of 15 cm H_2O in each case—i.e. 0 to + 15 cm and − 5 to + 10 cm. The speed of inflation was the same.

A cinematograph film of the manometer was taken and a complete cycle of the machine under both sets of conditions analyzed. The manometer readings were then plotted against time and the

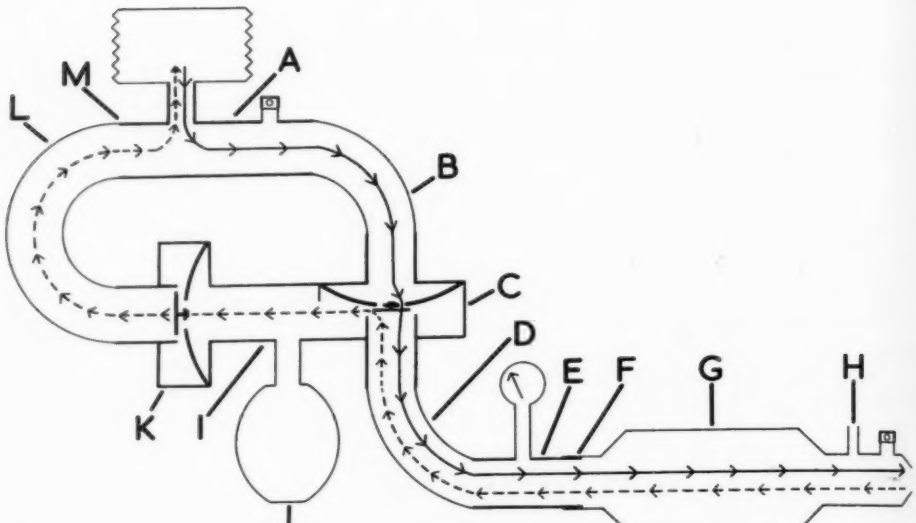


FIG. 1
Diagram of the modified circuit.

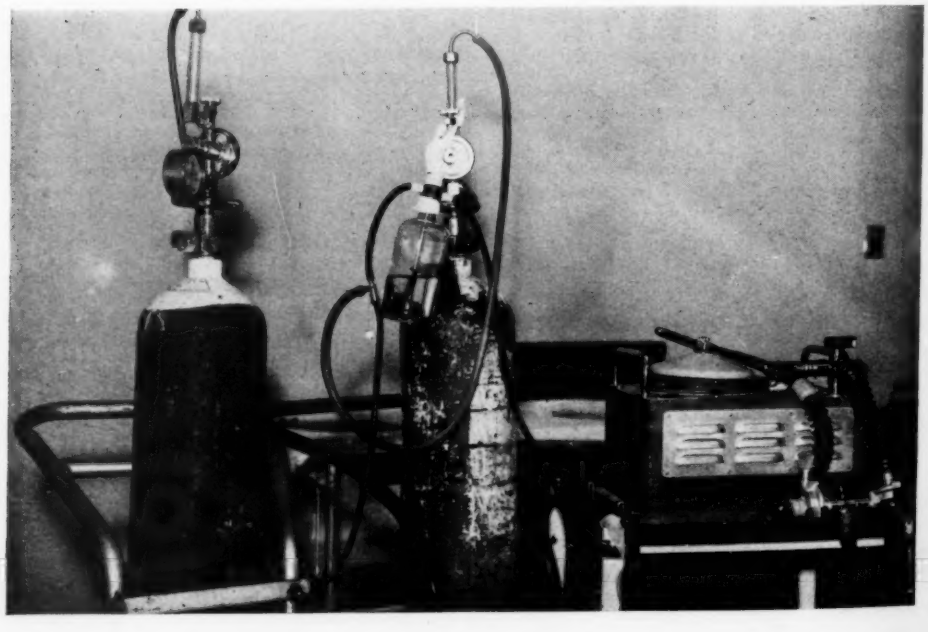


FIG. 2
Photograph of modified machine.

graph representing the changes in pressures drawn. This is shown in figure 3.

The mean intrathoracic pressure calculated from the film was 5.9 cm H_2O in the unmodified machine and 1.2 cm H_2O in the modified, a most significant reduction.

The modified machine has been used with success in routine operations, maintaining patients on nitrous oxide and oxygen (in the thiopentone-relaxant-pethidine-nitrous oxide method), also using air enriched with oxygen to maintain respiration in hibernated patients and in long term respiratory paralysis. The air supply is from a cylinder of compressed air. An oxygen flowmeter was used as one calibrated for air was not obtainable. The error is under 10 per cent.

In long term cases the use of a closed circuit with a small leak minimizes the problem of humidification, as moisture is conserved in the circuit. Some condensation occurs in the corrugated tube (fig. 1D) but the inspiratory-expiratory valves remain dry and function perfectly. They have needed no attention even after 72 hours of continuous use.

This machine must not be used with explosive gases.

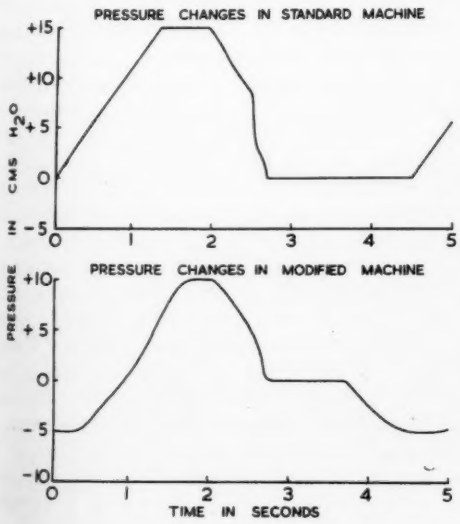


FIG. 3

Graphs of pressure changes in modified and standard machine. The speed of the machine was constant. Note in modified graph: (*a*) Slight delay in rise of pressure as small leak occurs into bag (J) before valve (K) acts. Thus a shorter positive phase. (*b*) Peak pressure is maintained for a shorter time. This pressure is maintained while excess gasses are blown off through the expiratory valve. Less gasses are blown off in the modified machine.

ADVANTAGES OF A SUBATMOSPHERIC PRESSURE IN EXPIRATORY PHASE

A fit person compensates for intermittent positive pressure by increasing the venous pressure. At operation this raised venous pressure leads to a great increase of bleeding, especially troublesome oozing. A lowering of the mean intrathoracic pressure decreases greatly the haemorrhage, easing the operation and leaving a fitter patient.

The frail, the ill, and those upon whom hypotensive drugs have been used cannot compensate for the raised intrathoracic pressure. I.P.P. respiration may, in these cases, cause a precipitate drop in blood pressure due to the interference with the venous return.

The introduction of a subatmospheric pressure phase in these cases leads to an immediate increase in the venous return and an improvement in the blood pressure. I have, in these cases, seen the blood being sucked out of the larger veins during operation, while the pressure has been subatmospheric.

In the grossly emphysematous patient the elasticity of the lungs disappears and I.P.P. leads to gross dilation of the lungs, interference with the venous return, and collapse of the patient.

A subatmospheric phase leads to rhythmical inflation and collapse of the lungs and restoration of the patient's condition. In these cases the lungs do not deflate by themselves and the rebreathing bag (fig. 1J) never fills, the lungs being emptied by the negative pressure exerted by the bellows of the machine.

SUMMARY

A simple, inexpensive modification of the Beaver Respirator is described. It introduces a subatmospheric phase, prevents the valves failing through condensation, and minimizes humidification problems in long term cases. A method of calculating intrathoracic pressure, the working, and use of the machine are also described.

ACKNOWLEDGMENTS

I wish to thank Mr. J. Hainsworth of the St. James's Hospital Photographic Department for his help with the photographs and diagrams. Also Mr. W. Wilson, Senior Anaesthetic Technician at St. James's Hospital, for his help and patience while assembling the apparatus.

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CORRESPONDENCE *continued from page 182*

patient lived for nine hours after the operation and inflation with oxygen was carried on during this period. On three occasions, at two, four and eight hours after the operation, he quite spontaneously showed signs of returning muscle tone and increased depth of respiration. These lasted for about five minutes on each occasion and he then relapsed into the picture of partial curarization that he had shown since the end of the operation. His B.P. was maintained until just before his death.

The story in this case was complicated by the fact that at operation there was some question of injury to the right pleura. Some six hours after surgery he developed clinical signs of a right haemo-pneumothorax which was confirmed radiologically. A needle was inserted into the right chest and a little air and some 36 ounces (1 litre) of bloodstained fluid were withdrawn. The air was not under tension.

At autopsy there was evidence of a pneumothorax on the left but not on the right, this again was not under tension. Both lungs showed areas of collapse and the growth was found to be extending into the posterior pericardium and the right lower lobe.

Any definite conclusions cannot, of course, be drawn from one case and the story of the second anaesthetic contains many other complicating factors. Yet this patient showed signs of neostigmine-resistant curarization for at least five hours after the final dose of curare and also the total dose of d-tubocurarine (35 mg) was considerably less than anticipated for a four-hour thoracotomy. One week previously the use of gallamine followed by neostigmine had not been attended by any unexpected reaction. If a deficiency of potassium was a cause of this condition the deficiency presumably arose as a result of failure to ingest enough food on account of his dysphagia. Should this have been the case then an abnormal response to the use of gallamine at oesophagoscopy would have been expected. His daily intake of potassium between the anaesthetic procedures was certainly adequate and the biochemical investigations reveal no abnormality. Unfortunately at no time during his stay in hospital was an e.c.g. taken. Certainly the magnitude of the surgical procedures undertaken shows great variation, but the patient's condition during the oesophagectomy caused no alarm and there is no obvious reason why he should have failed to respond to neostigmine at the end of the operation. There was no gross dehydration or evidence of electrolyte imbalance as is seen in cases of long standing intestinal obstruction and allied conditions.

In brief it is difficult to see that there was any deficiency of potassium in this patient to account for this sequela of the second anaesthetic.

R. A. L. LEATHERDALE
United Oxford Hospitals

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ON CHLOROFORM AND OTHER ANÆSTHETICS

THEIR ACTION AND ADMINISTRATION

BY

JOHN SNOW, M.D.

Licentiate of the Royal College of Physicians

(*Continued from page* 144)

MODE OF DEATH IN THE ACCIDENTS FROM CHLOROFORM

In all the cases in which the symptoms which occurred at the time of death are reported, there is every reason to conclude, as shown above, that death took place by cardiac syncope, or arrest of the action of the heart. In forty of these cases the symptoms of danger appeared to arise entirely from cardiac syncope, and were not complicated by the over-action of the chloroform on the brain. It was only in four cases that the breathing appeared to be embarrassed and arrested by the effect of the chloroform on the brain and medulla oblongata, at the time when the action of the heart was arrested by it; and only in one of these cases (No. 42) that the breathing was distinctly arrested by the effect of the chloroform, a few seconds before that agent also arrested the action of the heart.

It was previously shown that chloroform vapour has the effect of suddenly arresting the action of the heart when it is mixed with the respired air to the extent of eight or ten per cent., or upwards; and we must therefore conclude that, in the fatal cases of its inhalation, the air the patients were breathing just before the accidents occurred contained this amount of vapour. There was no means adopted, so far as is reported, to regulate the proportion of vapour in the inspired air, in any case in which an accident happened; and there was the liability in every case that ten per cent. or more of vapour might be present in the air the patient breathed; and in no case did death occur in the manner that it occurs when the vapour of chloroform does not exceed five per cent. of the inspired air.

There is in a great number of the cases an evident connection between the accident and the probable strength of the mixture of vapour and air. In six cases the accident occurred just after the commencement of the inhalation; in two of the cases, Nos. 27 and 37, the fatal symptoms occurred just after fresh chloroform had been applied on the handkerchief and sponge; and in several cases, in which the circulation was suddenly arrested just after the patient had been rendered insensible, the insensibility had been induced so quickly as to prove that the vapour must have been inhaled in a very insufficient state of dilution.

THE TWO KINDS OF SYNCOPE

Dr. Patrick Black has made an objection to the fact of the patients having died of paralysis, or over-narcotism of the heart, in the accidents from chloroform.* He says that paralysis of the heart would be death by syncope, but that the symptoms before death, and the conditions of the organs met with afterwards, are not in accordance

* Chloroform: How shall we ensure Safety in its Administration ? Pamphlet. London: 1855.

with such a view of the case. In order to show that both the symptoms and the after death appearances, in the fatal cases of inhalation of chloroform, are consistent with paralysis of the heart, it is necessary to point out the difference between ordinary syncope and cardiac syncope. One of the best examples of ordinary, or what may be called anæmic syncope, is that which occurs in a common blood-letting, whilst the patient is in the sitting posture. When the bloodvessels, especially the veins, which at all times contain the greater part of the blood in the body, do not accommodate themselves fast enough to the diminished quantity of blood, the right cavities of the heart are supplied with less and less of the circulating fluid; and in a little time are not supplied at all, when the heart ceases to beat, in accordance with the observation of Haller, that it does not pulsate when it is not supplied with blood. The moment the heart ceases to supply blood to the brain there are loss of consciousness and stoppage of respiration; but on the patient being placed in the horizontal position the blood flows readily into the right cavities of the heart from the great veins of the abdomen and lower extremities; the heart immediately recommences its contractions; the brain is again supplied with blood, and respiration and consciousness return.*

The blood may remain in the ordinary quantity; but if the bloodvessels do not keep up their usual support, and exert a sufficient pressure on their contents, the same kind of syncope will occur as that from blood-letting. The late Sir George Lefevre related the case of a lady who fainted whenever she left her bed, and assumed the upright posture; no cause could be found for this until it was ascertained that she suffered from varicose veins of the legs: bandages to these extremities prevented the fainting. It is obvious that in this case the mechanism of the syncope was the same as that in blood-letting; the distension of the varicose veins under the weight of the superincumbent blood had the same effect in preventing the supply to the right cavities of the heart, as if the blood had been entirely removed. The faintness which often occurs on first rising, when a person has long kept the recumbent posture from any local cause, is probably of the same kind; the veins not having had to support the weight of the usual column of blood for some days or weeks, lose their tone we may presume, and yield when they are all at once subjected to the weight of a column of blood extending from the lower extremities to the heart, so that this organ ceases to be properly supplied with the circulating fluid.

In cardiac syncope, on the other hand, the cavities of the heart, or at all events the right cavities of this organ, are always full, whether the syncope depend on paralysis of the heart by a narcotic, or inherent weakness of its structure, or on its being overpowered by the quantity of blood with which it is distended. After death from this kind of syncope, if the blood has not been displaced by artificial respiration or

* See some interesting papers on the value of recumbent position in syncope, by Dr. Richardson, in the *Association Medical Journal* for 1854. I entirely agree with Dr. Richardson that no kind of syncope commences at the brain, and that, during recovery, the heart always resumes its functions before consciousness is restored. The restoration of the heart's action in ordinary syncope by the re-supply of blood to its cavities, without any alteration in the condition of the brain, was well proved by Dr. Richardson by means of some interesting experiments on animals which I had the opportunity of witnessing.

other causes, the right cavities of the heart and the adjoining great veins will be found filled with blood, and the lungs will in many cases be more or less congested. The appearances in short will be very much the same as in asphyxia by privation of air, which ends in a kind of cardiac syncope, the stoppage of the heart being partly due to over-distension of its right cavities, and partly to loss of power in its structure, from the want of a supply of oxygenated blood through the coronary arteries. In death by anæmic syncope, on the contrary, all the cavities of the heart are found empty, or nearly so, and the same is frequently the case with the adjoining great veins, whilst the lungs are usually pale.

The syncope occasioned by some kinds of mental emotion is of the ordinary or anæmic kind, and consequently the condition of the brain must act first on the bloodvessels, and not directly on the heart. Certain persons are liable to faint on witnessing a surgical operation. Now if the mental emotion of these persons acted directly on the heart, whilst the rest of the vascular system was unaffected, the distribution of the blood would be nearly the same as in asphyxia, where the circulation is first impeded in the lungs, and is ultimately arrested by loss of power in the heart. If the action of the heart were weakened, or stopped, in the first instance, by the kind of emotion under consideration, the arteries would be emptied by their contractility and elasticity, and the blood would accumulate in the right cavities of the heart and the great veins leading to them. In a medical student fresh from the country, who is by no means deficient in blood, the jugulars would become distended and the face livid, and the recumbent posture would probably do but little towards removing the symptoms. The phenomena which are witnessed, however, indicate a very different condition of the vascular system. The person about to faint from the cause indicated, frequently becomes pale before he feels anything wrong; and when requested to retire and sit down, often says that there is nothing the matter with him. In a short time he faints, and falls, if no one catches hold of him; but the moment he is in the recumbent posture he recovers. In such a case as this, the effect of the mental emotion must first be exerted on the veins, or the veins and capillaries, through the nerves which supply these vessels; they allow themselves to become distended, and the heart ceases to act for want of its supply of blood, as in syncope from blood-letting, and anæmic syncope from any cause.

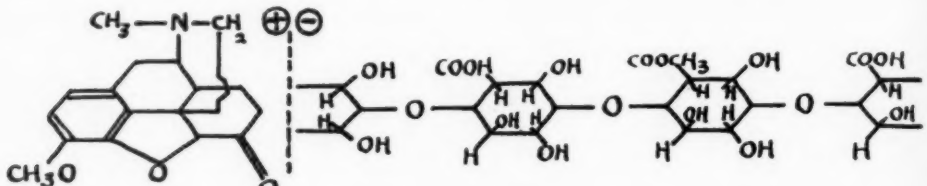
Several authors have attributed the empty state of the heart met with after death, in certain cases of fatal syncope, to want of power in the left ventricle to supply the right cavities of the heart; but this is to argue as if the blood passed out of the body after leaving the right ventricle, and the left ventricle had to supply a newly-formed fluid. The effects of want of power in the left ventricle are the same as those of an obstruction at the origin of the aorta; the lungs become congested; and the right cavities of the heart more or less distended, from the blood not being able to pass readily through the lungs. Patients who die of heart disease die with the cavities of that organ full. Some patients, indeed, with fatty disease of the heart, die suddenly of anæmic syncope, and the heart is found empty; but in these cases it is evident that death is not

[Continued on page 192

PRELIMINARY COMMUNICATION

CLINICAL TRIAL OF NEW ANALGESIC

Sir,—Recently a new long-acting analgesic drug has been given preliminary clinical trials in this hospital. The drug, diagrammatically represented below, is the pectinate of dihydro-hydroxy-codeinone, the pharmacology of which has been studied in France (Aubry, 1953).



The investigation here was divided into two parts: first, the use of the drug as premedication in place of morphia and pethidine, etc. The patients were selected at random; no great variation in age or severity of illness was sought, the cases ranging from hernia to nephrectomy, in the adult age groups. A fixed dose of 10 mg of dihydro-hydroxycodeinone pectinate (Proladone) was given intramuscularly one hour before operation, atropine in suitable doses also being administered. The normal effect of premedication, the production of sedation and the reduction of the total amount of anaesthetic agent used, was absent and the drug proved unsatisfactory. This was contrary to the findings of Mandel (1954).

It became obvious from the first few patients given the drug that it had a very prolonged action, not one patient in the whole of this first series of eighteen requiring any analgesic whatsoever in the fourteen hours immediately after operation. The anaesthetic sequence used was that normally employed, the patients recovering within the hour after operation.

After these totally unexpected results it was decided that to proceed further with this part of the trial was useless and the second part of the trial was commenced. Patients were now given normal premedication, morphia, papaveretum or pethidine, and atropine or scopolamine, and the anaesthetic was that usually administered. Dihydro-hydroxycodeinone pectinate, 10 mg intramuscularly, was given either in the theatre or immediately on return to the ward. Selection was as before, and the results are given below.

Effect of Dihydro-hydroxycodeinone Pectinate in 100 *Patients*

Type of operation	Upper abdomen gastrec-tomy cholecyst.	Lower abdomen hyster.	Other abd. gut resect. appendix	Nephrec-tomy	Herniae	Thyroid	Other	Total
Number of cases	21	20	11	7	19	8	14	100
Number of cases of nausea and/or vomiting	3	12	2	1	1	1	2	22
Cases requiring further analgesics	8	9	4	2	–	–	–	23

Number of patients requiring no further postoperative analgesic = 77.

In 23 patients given dihydro-hydroxycodeinone Pectinate further analgesic drugs were needed in:				
1 case	within	2	hours of	dihydro-hydroxycodeinone
5 cases	,,	4	,, ,,	,,
2 ,,	,,	6	,, ,,	,,
5 ,,	,,	8	,, ,,	,,
5 ,,	,,	10	,, ,,	,,
3 ,,	,,	14	,, ,,	,,
2 ,,	,,	18	,, ,,	,,

These results bear out the original French statement that this drug is a long-acting analgesic (Truchard, 1954), its effects lasting from eight to twelve hours. Further trials are in progress, the use of the drug in children and in malignant disease being investigated. I am grateful to Messrs Crookes Laboratories for their generous supply of the drug (Proladone).

O. H. BELAM,
*Whittington Hospital, London, N.*19.

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PRELIMINARY COMMUNICATION

A NEW HAEMOSTATIC DRUG

Sir,—From time to time attempts are made to reduce haemorrhage at operation by the pre-operative administration of drugs which lower the clotting time. A drug with this property has recently been introduced to this country. This is sodium-α-naphthylamine-4-sulphonic acid or "Naphthionin S.N.S."

"Naphthionin S.N.S." is chemically related to Congo Red. The way in which it reduces the clotting time is not known for certain, but it probably stimulates the production of fibrinogen and thromboplastin by the reticulo-endothelial system. The drug is administered intravenously (100 mg in 10 ml) and its effect reaches a peak 1-3 hours after injection. Several authors have reported successful clinical trials of the drug in reducing blood loss at operation. A similar trial carried out at the Queen Victoria Hospital, East Grinstead may be of interest to your readers.

Clinical trial.

One hundred dental operations performed at the Queen Victoria Hospital, East Grinstead, between November 23, 1955, and February 10, 1956, were used for the survey (table I).

TABLE I

Type of case used for survey	Number
Removal of wisdom teeth	48
Multiple extractions and dental clearance	34
Removal of buried roots	5
Removal of buried teeth	4
Removal of dental cysts	5
Insertion of Gunnings splint and wiring	1
Removal of fibroma of palate	1
Antrostomy	1
Alveolectomy	1
Total	100

Certain dental cases admitted between these dates were not used for the survey, e.g. (1) major operations in which controlled hypotension was used; (2) children under 15 years of age; (3) miscellaneous cases inadvertently left out.

There was no selection of cases apart from this. Ages varied from 17 to 86. Several had intercurrent conditions such as hypertension, coronary disease, and chronic bronchitis.

The 100 cases were arbitrarily divided into two groups of 50. The patients in one group (A) all received 100 mg of " Naphthionin S.N.S." intravenously 1 to 3 hours pre-operatively. Those in the second group (B) did not. During each operation the dental surgeon was asked to assess the amount of bleeding and to state whether it was average, more than average, or less than average. This assessment was made on: (*a*) the number of swabs used; (*b*) the amount of blood in the sucker bottle; (*c*) general impressions of operating field. The surgeons were not aware of the group to which each patient belonged. The results are given in table II.

Some of these cases were retained in hospital for more than 24 hours owing to bruising and swelling of the jaws. The incidence of this complication in Group A was 18 per cent and in Group B 20 per cent. No toxic side effects of the drug were noticed in any of these cases.

TABLE II

Bleeding	Group A (Received Naphthionin S.N.S.)		Group B (Received no Naphthionin S.N.S.)	
Average	19	38%	29	58%
More than average	11	22%	6	12%
Less than average	20	40%	15	30%
Totals	50		50	

TABLE III

Bleeding	Group A (Received Naphthionin S.N.S.)		Group B (Received no Naphthionin S.N.S.)	
Average	4	20%	11	55%
More than average	4	20%	3	15%
Less than average	12	60%	6	30%
Totals	20		20	

A further 20 cases have since been given 200 mg (double the previous dose) of " Naphthionin S.N.S." and compared with a control group of 20. In this series, Naphthionin appeared to have a rather more pronounced effect on the bleeding (table III).

Some of the patients receiving 200 mg of " Naphthionin S.N.S." complained of a sensation of heat all over the body and constriction of the chest. These symptoms were not accompanied by objective signs and always disappeared in about 5 minutes.

Discussion.

Two points seem to emerge from this survey:

(*a*) " Naphthionin S.N.S." appears to be quite safe in the doses mentioned.

(*b*) The percentage of cases in which bleeding was thought to be less than average was higher in the group receiving the drug than in the control group.

More objective experiments will be required to determine the degree to which bleeding can be reduced at operation by the use of " Naphthionin S.N.S."

A. J. HEBER
East Grinstead

ON CHLOROFORM AND OTHER ANAESTHETICS *continued from page* 189

occasioned by the disease of the heart, but by some condition of the bloodvessels which accompanies it.

Chevalier was, I believe, the first to draw marked attention to cases of sudden death arising from an empty state of the heart, in a paper in the first volume of the *Transactions* of the Royal Medical and Chirurgical Society; and he rightly attributed the emptiness of the heart to a loss of power in the blood vessels. His words are as follows: —

" The disease I have now described may, perhaps, be termed *asphyxia idiopathica*. The essential circumstances of it evidently denote a sudden loss of power in the vessels, and chiefly in the minuter ones, to propel the blood they have received from the heart. In consequence of which, this organ, after having contracted so as to empty itself, and then dilated again, continues relaxed for want of the return of its accustomed stimulus, and dies in that dilated state."

(*To be continued*)

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VOLUME XXIX No. 4 *Published monthly* APRIL 1957

Annual subscription (post free): Inland £3 15s.; Overseas £4 4s.; U.S. and South Americas $12.00

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